No. 23-10640

UNITED STATES COURT OF APPEALS
FOR THE ELEVENTH CIRCUIT

BRADLEY SANDERS, ET AL.,
Plaintiffs-Appellants

v.

AJANTA PHARMA USA, INC., ET AL.,
Defendants-Appellees

IN RE: ZANTAC (RANITIDINE) PRODUCTS LIABILITY LITIGATION

On Appeal from the United States District Court
for the Southern District of Florida

PERSONAL INJURY PLAINTIFFS-APPELLANTS' OPENING BRIEF

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CERTIFICATE OF INTERESTED PERSONS

Pursuant to Eleventh Circuit Rule 26.1-1, counsel for Plaintiff-Appellants hereby certifies that the previously filed Certificate remains correct.

Dated: April 10, 2024

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STATEMENT REGARDING ORAL ARGUMENT

Appellants respectfully request oral argument because this appeal turns on complex issues of law and fact that were decided over multiple years in the proceeding below. Oral argument will assist the Court in resolving the issues for many thousands of cases.

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STATEMENT REGARDING ADOPTION OF BRIEFS OF OTHER PARTIES

The Personal Injury Appellants adopt the arguments set forth in the brief for the Generic-Only Plaintiffs in its entirety.

STATEMENT OF JURISDICTION

This Court has appellate jurisdiction under 28 U.S.C. §1291 because the district court entered final judgments. Federal subject matter jurisdiction in the district court was not proper under 28 U.S.C. §1332 because the district court destroyed complete diversity by merging the cases.

INTRODUCTION

This multidistrict litigation went off the rails after the district court decided (based on its own view of the science) that Zantac does not *really* cause cancer. Discerning whether a *Daubert* court improperly weighed the science rather than evaluating the reliability of the experts' methods can often be difficult. Here, the district court said the quiet part out loud. It was not content to answer the actual question posed by Rule 702: whether designated experts reliably applied their scientific disciplines to reach opinions that many, including the district court, may disagree with. Instead, the district court adjudicated once and for all, based on "its own understanding" of the science "the theoretical potential of ranitidine to cause cancer." MDL.Dkt.6622 at 5.[1] And because the district court's "own understanding" was "the same for every Plaintiff," *id.*, the district court applied its scientific conclusion to all MDL Plaintiffs, including those who filed suit *after* the district court's *Daubert* decision.

The district court would not even entertain the possibility that these later-filed Plaintiffs could disclose *different* experts who could reliably apply their scientific methods to show general causation. Having weighed the science for itself, the district court came to a definitive answer to the ultimate question. But Rule 702

[1] This brief refers to MDL docket entries as "MDL.Dkt."

casts the district court in the modest role of gatekeeper. Its attempt to play the starring part of scientific arbiter must be reversed.

This litigation began when thousands of plaintiffs sued the manufacturers and sellers of Zantac after the public learned that it degrades into NDMA, which the FDA itself described as "a probable human carcinogen (a substance that could cause cancer)"[2] and which one of the Defendants itself (quoting the World Health Organization) described as "highly likely" to be "carcinogenic to humans, potentially at relatively low levels of exposure." MDL.Dkt.6164-10 at 78. (GSK Health Hazard Assessment).

The district court ended claims against makers of generic ranitidine at the Rule 12 stage. The district court agreed—as it must—that Zantac was misbranded and therefore illegal to sell under federal law. But it nonetheless held that state law prohibiting the sale of unsafe drugs somehow conflicted with federal law, ruling for Generic Defendants on all claims. After Plaintiffs amended the complaint to plead claims limited to the failure to take steps that Generic Defendants undisputedly could have taken unilaterally—such as changing expiration dates—the district court again dismissed the claims. This time, the reasoning was that Defendants could not take

[2] Press Release, FDA, FDA Requests Removal of All Ranitidine Products (Zantac) from the Market (Apr. 1, 2020), https://www.fda.gov/news-events/press-announcements/fda-requests-removal-all-ranitidine-products-zantac-market.

all steps state law demanded, and so preemption applied even to the claims based on steps they could have taken.

Consumers of generic ranitidine who sued the Brand Defendants on a negligent misrepresentation theory fared even worse. Even though a super-majority of state supreme court justices have *endorsed* the theory, the district court placed a weighty thumb on the scale against it, predicting that *no* states outside the two in which their supreme courts had spoken would allow negligent misrepresentation claims. That included Illinois, even though every previous case applying Illinois law—in both state and federal court—has ruled that the Illinois Supreme Court would allow the claim. Next, the district court ruled—contrary to every other court to consider the question—that even claims under California law fail for lack of personal jurisdiction, in effect ruling the theory a dead letter for any drug maker who is not headquartered in California.

After the motions to dismiss, Plaintiffs' Leadership disclosed a slate of highly credentialed experts on general causation for the remaining claims against the Brand Defendants. Since the FDA's recall of ranitidine, every state court to decide the issue has admitted expert testimony that NDMA in ranitidine can cause cancer. A federal court admitted expert testimony that a different drug with NDMA in it can cause cancer. *In re Valsartan, Losartan, & Irbesartan Prods. Liab. Litig.*, No. 19-MD-2875, ECF No. 1958 (D.N.J. Mar. 4, 2022). Independent scientists have

concluded that "the *clear data* from our real-world observational study *strongly support* the pathogenic role of NDMA contamination [in Zantac], given that long-term [Zantac] use is associated with a *higher likelihood of cancer development*." MDL.Dkt.6061-6 (Wang) at 12 (emphasis added). Yet the district court here held that *no* expert could opine that NDMA in ranitidine can cause cancer.

If that sounds unusual—it is. *See* MDL.Dkt.6120 at 7 (acknowledging that the order might be "surprising" in light of the FDA recall). To Appellants' knowledge, a district court has never forbidden an expert from testifying that a substance causes a disease after an FDA recall based on concerns that this same substance causes that disease—let alone after multiple human epidemiology studies reported a link between the drug and the disease. The district court's decision stands alone.

The district court's *Daubert* order resulted from its fundamental misunderstanding of its gatekeeping role. The court believed its role was to decide causation simpliciter, *i.e.*, to determine "the theoretical potential of ranitidine to cause cancer." MDL.Dkt.6622 at 5. But that is not the proper role of a *Daubert* court, which is not permitted to "take sides" on scientific debates like the one here. *Milward v. Acuity Specialty Prods. Grp.*, 639 F.3d 11, 22 (1st Cir. 2011). The sheer length of the district court's 341-page opinion—the most prolix *Daubert* decision in

the federal reporter—is precisely because the district court decided the *ultimate* factual question of causation.

This Court can be perfectly sure that the district court found for itself that the science does not link Zantac to cancer—rather than that the designated experts deployed unreliable methods—because it refused to allow plaintiffs who filed suit *after* the *Daubert* order to come forward with experts of their own. And it applied its *Daubert* order after-the-fact to Generic, Distributor, and Retailer Defendants, who never even briefed or argued any Rule 702 issues after obtaining dismissal under Rule 12. So much for our adversarial system. The district court's approach makes sense only if it definitively decided causation. There is no reason to waste time or resources permitting any Plaintiff to proceed against any Defendant if the district court had already determined, once and for all, that *no* Plaintiff could prove general causation.

To reach its unprecedented result, the district court committed multiple errors of law. First, the district court ignored the rule that, when a substance is known to cause a disease—as NDMA is known to cause cancer—no extensive *Daubert* analysis on general causation is required. *See McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1246 (11th Cir. 2005); *Chapman v. Procter & Gamble Distrib., LLC*, 766 F.3d 1296, 1314 (11th Cir. 2014) ("[I]f it were generally accepted by the medical community that [the substance] causes [the disease]," this "would eliminate the

Daubert analysis of the [plaintiffs'] experts."). The district court sidestepped this precedent by focusing myopically on ranitidine rather than NDMA. That was a classic level-of-generality error, as this Court's precedents confirm. *All* ranitidine breaks down into NDMA. NDMA is a carcinogen. Therefore, all ranitidine consumption exposes users to a substance that is known to generally cause cancer.

Second, the district court ignored the fact that the experts here relied on all three of the "primary methodologies" blessed by this circuit, any *one* of which is sufficient to reliably opine on general causation. These experts utilized the "background risk" methodology by relying on studies showing that "taking [Zantac] increases the risk of [cancer] beyond the usual incidence of [this] common disease[]." *McClain*, 401 F.3d at 1244. They relied on evidence that ranitidine produces a "dose response"—*i.e.*, that more ranitidine use led to more cancer—"the single most important factor to consider in evaluating whether an alleged exposure caused a specific adverse effect." *Chapman*, 766 F.3d at 1307 (citation omitted). And these experts relied on "epidemiology" showing that ranitidine use was associated with increased cancer rates—"the 'best evidence of causation' in cases involving toxic substances." *Id.* (citation omitted).

Third, the district court exceeded its gatekeeping role under *Daubert*, flouting this Court's instructions to "meticulously focus on the expert's principles and methodology, and not on the conclusions that they generate." *McDowell v. Brown*,

392 F.3d 1283, 1298 (11th Cir. 2004). From the outset, the district court "meticulously focus[ed]" entirely on the conclusions. Again and again, the district court hammered the theme that "no scientist outside this litigation [has] concluded ranitidine *causes* cancer." MDL.Dkt.6120 at 7 (emphasis added); *accord id.* at 6, 169, 177, 180, 228, 250, 259, 281, 299. That is frequently the case. Authors of *individual* studies are not weighing *all* of the scientific evidence, and so are often hesitant to conclude that an association is causal. But plaintiffs' experts did weigh all of the evidence deploying the time-tested methods of their scientific disciplines. It says precisely nothing about their fidelity to those methods to repeatedly observe that other scientists *who did not deploy those methods* did not reach the same conclusions. With conclusions as its focus, it is no surprise that the district court went straight into "evaluat[ing] the persuasiveness of competing scientific studies" for more than 100 pages. *Quiet Tech. DC-8, Inc. v. Hurel-Dubois UK Ltd.*, 326 F.3d 1333, 1341 (11th Cir. 2003) ("[I]t is not the role of the district court to make ultimate conclusions as to the persuasiveness of the proffered evidence.").

Finally, the district court's reasons for excluding particular experts—more than 20 purportedly distinct reasons—demonstrate that it acted not as a gatekeeper, but an "armed guard." *Ruiz-Troche v. Pepsi Cola of P.R. Bottling Co.*, 161 F.3d 77, 86 (1st Cir. 1998). For example, the district court "inferred" the level of reliance the experts placed on certain studies, MDL.Dkt.6120 at 260 n.135, decided that the

experts' reliance on certain studies was "undue," *id.* at 256, criticized experts for relying on any epidemiology study that had wide confidence intervals or failed to offer a conclusion about causation (something such studies never do), *id.* at 250, and added in multiple, analysis-free, catch-all "totality of the evidence" bases for exclusion, *id.* at 120, 158, 309, 321, 332.

Although a district court's thoroughness in most cases is a virtue, the district court here assumed "the role of St. Peter at the gates of heaven, performing a searching inquiry into the depth of an expert witness's soul," thereby usurping "the ageless role of the jury" in "evaluating witness credibility and weight of the evidence." *Allison v. McGhan Med. Corp.*, 184 F.3d 1300, 1321 (11th Cir. 1999) (citation omitted). This results-driven reasoning is on display throughout the opinion, but one need look no further than the section explaining the district court's "Final Ruling on Epidemiology Motion." MDL.Dkt.6120 at 298. There, the district court provided a "demonstrative" to illustrate why it excluded every expert. *Id.* The district court noted that the experts had deemed "influential" the Cardwell study—which demonstrated a statistically significant link between ranitidine and cancer. The district court *faulted* the experts for relying on that study, because the study's author had said "further studies should be performed," *id.* at 299, in a snip-quoted interview with *The Daily Mail*—an infamous tabloid from the United Kingdom whose other "science"-related articles have included *Big Headed Babies "More*

Prone to Cancer"; *Study Claims Women Choose Briefcase Over Baby if They Find It Hard to Attract Men*; and *EXCLUSIVE: Shocking Footage Shows "Cruel" Experiments Carried Out on Rodents at Taxpayer-Funded Lab in Oregon Where Animals Were Piled [sic] with up to 15 Bottles of Wine a Day, Forced to Fight and Chained to Cages*, and which is not even a valid source for use on the Wikipedia, much less the Federal Reporter.[3]

This is simply not the way *Daubert* is supposed to work. A district court judge cherry-picked the evidence, ignored an FDA recall, rejected multiple studies showing a link between Zantac and cancer based on its own intuition about what evidence deserves greater weight, and ultimately used a British *tabloid* to "demonstra[te]" why the jury was not allowed to hear valid expert testimony. *See* MDL.Dkt.6120 at 299 ("[T]he Court believes that this interview [in the Daily Mail] underscores the point."). This Court should reaffirm the admonition that judges must not trade their black robes for white lab coats.

[3] The district court was likely unaware of the provenance of this piece, which it repeatedly describes as an "article" and "interview" by a "journalist." MDL.Dkt.6120 at 299. Similarly, the court repeatedly used "salt" interchangeably with "sodium nitrite," apparently confusing the latter with sodium *chloride*. *E.g.*, *id.* at 3-5. But the risk of such embarrassing errors—and there are many here—is exactly why, when conducting a *Daubert* analysis, the district court should not attempt to "make ultimate conclusions as to the persuasiveness of the proffered evidence." *Quiet Tech*, 326 F.3d at 1341.

STATEMENT OF THE ISSUES

1. Did the district court lack diversity jurisdiction because the operative pleading included plaintiffs and defendants from the same states?

2. Did the district court err in dismissing claims due to preemption?

3. Did the district court abuse its discretion in excluding every general causation expert based on its own conclusions about the underlying scientific studies?

4. Did the district court violate due process in applying its *Daubert* ruling to later-filed plaintiffs who never agreed to use the experts the court had excluded?

5. Should the Court certify the long-muddled question of whether consumers of generic drugs can sue brand-name manufacturers under the laws of 32 jurisdictions?

6. Did the district court err in dismissing negligent misrepresentation claims for lack of personal jurisdiction, and, if not, should this Court vacate its merits ruling on the same claims?

STATEMENT OF THE CASE

A. Procedural History

This appeal arises from multidistrict litigation addressing claims based on ranitidine's propensity to degrade into NDMA, a genotoxic carcinogen. Before its withdrawal from the market in 2020, ranitidine was sold both over-the-counter (OTC) and by prescription, and was available in generic or branded form (the brand-

name is Zantac). Distributors, retailers, and pharmacies sold every kind of ranitidine. Generic Manufacturers ("Generic Defendants") manufactured generic ranitidine (both prescription and OTC). Brand-Name Manufacturers ("Brand Defendants") manufactured OTC and prescription Zantac. Thousands of Plaintiffs sued, naming each category of Defendant.

The district court dismissed all claims against the distributor, retailer, pharmacy, and Generic Defendants under Rule 12. MDL.Dkt.2512, 2513, 2532, 3716, 3750. It also dismissed all claims against Brand Defendants that were predicated on the consumption of generic ranitidine. MDL.Dkt.2516, 3719. Only the claims based on consumption of branded Zantac, against Brand Defendants, based on their failure to warn and negligence proceeded to summary judgment. MDL.Dkt.3717. Plaintiffs' leadership disclosed twelve experts to opine on general causation, whom the Brand Defendants moved to exclude under Rule 702. The district court requested that the parties directly send it full reports and deposition transcripts as they became available—months before briefing occurred.

B. The *Daubert* Ruling

Patients have been taking Zantac since it was first approved for treating ulcers in 1983. Even then, "the carcinogenicity of NDMA [wa]s established."[4] NDMA is

[4] Agency for Toxic Substances and Disease Registry (ATSDR), *Toxicological Profile for N-Nitrosodimethylamine* (2022); *see also* IARC, *IARC* Monographs on

recognized around the world as a probable human carcinogen; its only use is to intentionally cause cancer in animals. Before this litigation, Defendants themselves acknowledged that "NDMA is a genotoxic carcinogen," MDL.Dkt.6164-10 at 78, *i.e.*, a substance that causes cancer by causing damage to a cell's DNA.[5] For these types of carcinogens, scientists widely believe there is no safe dose.[6]

In 2019, independent pharmacies discovered NDMA in Zantac and other drugs, including a blood-pressure medication called Valsartan. For Zantac, Defendants' own testing revealed that this was not the result of contamination. MDL.Dkt.6155-14 at 65. Instead, the ranitidine molecule itself degrades into NDMA as a matter of basic chemistry, and does so more quickly when exposed to

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the Evaluation of Carcinogenic Risk of Chemicals to Man, vol. 17. IARC, Lyon, France, 125-75, 1978 (NDMA "is carcinogenic in all animal species tested" and "should be regarded for practical purposes as ... carcinogenic to humans"); U.S. Department of Health and Human Services, National Toxicology Program (NTP), *Report on Carcinogens* (2d ed. 1981) (NDMA is "reasonably anticipated to be a human carcinogen"); EPA, *Technical Fact Sheet: N-Nitroso-dimethylamine* (NDMA) (Nov. 2017) (flagging NDMA as a carcinogen).

[5] MDL.Dkt.6164-4 (Ciociola Dep.) at 171:11-14 (Pfizer: "I'm aware that NDMA is a carcinogen" and "no level would be an acceptable level of NDMA"); MDL.Dkt.6164-6, (Kugel Dep.) at 25:9-13 (Sanofi: admitting NDMA is "a potent carcinogenic"); MDL.Dkt.6164-12, (Hobbiger Dep.) at 58:16-21 (same).

[6] *See, e.g.*, Brambilla, et al., *Dose-Response Curves for Liver DNA Fragmentation Induced in Rats by Sixteen N-Nitroso Compounds as Measured by Viscometric and Alkaline Elution Analyses*, 47 Cancer Res., 3485-91 (1987) ([T]heoretically, the cancer causing mutation to the genetic material of the cell can be produced by any one molecule of certain chemicals."); *In re TMI Litig.*, 193 F.3d 613, 726 (3d Cir. 1999), *amended*, 199 F.3d 158 (3d Cir. 2000) ("[S]cientists assume that there is no threshold for the induction of cancer."); *Reference Manual* at 642.

high heat and humidity. *Id.* After the FDA and Defendants confirmed that every ranitidine pill would degrade into NDMA, the FDA recalled ranitidine from the market on the explicit basis that ranitidine ingestion could cause cancer. MDL.Dkt.6154-10; *see* MDL.Dkt.6120 at 3.

The FDA similarly recalled NDMA-contaminated Valsartan. MDL.Dkt.6182 at 224. Numerous plaintiffs filed suit against the makers of Valsartan, and the cases were consolidated in MDL 2875. Rejecting the *Daubert* challenge—regarding a drug containing the same carcinogen as Zantac—the Valsartan MDL court noted the Defendants' statements confirming that NDMA is a carcinogen, and asked "why is more even required?" MDL.Dkt.6182 at 224. The Court went on to state that "the association element has been clearly demonstrated, both through all the action by the government agencies [about Valsartan] and through the words of the defendants themselves [about NDMA]." *Id.* at 226.

Following the FDA-mandated market withdrawal in 2020, scientists around the world compared the cancer rates between people who took ranitidine and those who did not. Although the magnitude of the results varied by study and by cancer, even Defendants do not dispute that, in multiple studies, the patients who took ranitidine developed cancer at higher rates than those who did not. For example, one study showed that patients who took ranitidine had a 22% increased risk of bladder cancer. *See* MDL.Dkt.6185-31 at 7 (Cardwell). Another study showed that

patients who took ranitidine had a 35%, 26%, 27% and 22% increased risk of developing pancreatic, stomach, esophageal, and liver cancer, respectively. MDL.Dkt.6061-6 at 8 (Wang).

Consistent with these ranitidine studies, the studies about NDMA, and the FDA's action with respect to Zantac and Valsartan, the experts here testified that ranitidine could cause cancer. These eminent experts included Drs. Anne McTiernan, Patricia Moorman, Andrew Salmon, Jennifer Le, Dipak Panigrahy (who also testified in *Valsartan*), Errol Zeiger, Ronald Melnick, and Paul Michaels ("the experts").

The text of Rule 702 sets up four requirements:

> A witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if the proponent demonstrates to the court that it is more likely than not that:
>
> (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
>
> (b) the testimony is based on sufficient facts or data;
>
> (c) the testimony is the product of reliable principles and methods; and
>
> (d) the expert's opinion reflects a reliable application of the principles and methods to the facts of the case.

Fed. R. Evid. 702. This appeal comes down to 702(d): the reliable application of the methods to the facts. On that prong, the district court judge erred by swapping the

judicial robe for a lab coat and weighing the science for herself. That fundamental error underlies the entire order.

There is no question that the experts are eminently qualified. Dr. McTiernan is a full professor of epidemiology with a host of publications, a Ph.D. in epidemiology and an M.D., and she has been a member of an IARC Expert Working Group analyzing cancer. MDL.Dkt.6171-9 at 9-12. Dr. Moorman has published extensively on cancer, has a Ph.D. in epidemiology, and taught at Duke University Medical School for decades on cancer epidemiology and evidence-based medicine. MDL.Dkt.6179-6 at 3-4. Dr. Salmon is a toxicologist who worked for the California Environmental Protection Agency for more than 30 years, performing hazard assessments for carcinogens and teaching students at Stanford, U.C. Berkley, Davis, and Los Angeles. MDL.Dkt.6185-5 at 6, 332. Dr. Le is a board-certified pharmacotherapeutic specialist with experience in clinical pharmacology, pharmacovigilance, and patient outcomes associated with medication use. MDL.Dkt.6171-5 at 3-4. Dr. Panigrahy is a specialist in tumor dormancy and his award-winning laboratory studies the key characteristics of carcinogens. MDL.Dkt.6185-2 at 8-12. Dr. Michaels is a board-certified medical doctor and pathologist with publications on pancreatic cancer and tumor pathology. MDL.Dkt.6179-4 at 3, 70-71. These specialties are obviously helpful to the question of general causation.

All the experts relied on sufficient facts and data. To look for a link between ranitidine and cancer, these experts reviewed "epidemiologic studies," both for ranitidine and NDMA. MDL.Dkt.6171-9 at 14 (McTiernan); *see also e.g.*, MDL.Dkt.6179-6 at 7-8 (Moorman); MDL.Dkt.6185-5 at 53-62 (Salmon). They also reviewed "clinical, pathological, and biologic and mechanistic evidence regarding ranitidine, NDMA, and cancer development." MDL.Dkt.6171-9 at 14 (McTiernan); *see also e.g.*, MDL.Dkt.6179-6 at 7-8 (Moorman); MDL.Dkt.6185-5 at 53-62 (Salmon). In line with authoritative bodies like IARC, the experts followed a "weight of the evidence approach." *E.g.*, MDL.Dkt.6171-9 at 18 (McTiernan); *see Milward*, 639 F.3d at 18-19 ("No serious argument can be made that the weight of the evidence approach is inherently unreliable."). In employing this approach, the experts evaluated *all* the epidemiology studies performed on NDMA or ranitidine. They then applied their "informed judgment" to "interpret[] the results of [those] studies." *Milward*, 639 F.3d at 18 n.8.

The experts' principles and methods were unimpeachable. In support of their opinion, the experts pointed to "epidemiology," a primary methodology blessed by this Court. *Chapman*, 766 F.3d at 1308; *e.g.*, MDL.Dkt.6171-9 at 17 (McTiernan) ("This review assessed relevant published epidemiologic evidence on the association between use of ranitidine, exposure to other sources of NDMA, and risk of developing cancer."); MDL.Dkt.6179-6 at 7 (Moorman) (she "comprehensively

review[ed] and summarize[d] the epidemiologic evidence" and assessed "based on the totality of evidence from epidemiologic investigations as well as laboratory and mechanistic studies" whether "ranitidine use causes cancer in humans"). They relied on "dose response," another primary methodology. *Chapman*, 766 F.3d at 1308; *e.g.*, MDL.Dkt.6171-9 at 18 (McTiernan) ("I base this opinion on … the evidence of a positive dose-response effect."); MDL.Dkt.6185-5 (Salmon) (referencing "dose-response" more than 60 times). And they relied on background risk, another primary methodology that entails a showing "that taking [the substance in question] increases the risk of [the relevant disease] beyond the usual incidence of" the disease. *McClain*, 401 F.3d at 1244; MDL.Dkt.6171-9 at 18 (McTiernan) ("I base this opinion on the elevated risk estimates ... for use of ranitidine."); MDL.Dkt.6179-6 (Moorman) (discussing "risk estimates" throughout).

After reviewing the supporting literature and explaining why it showed an association between ranitidine, NDMA, and cancer, the experts then performed a "Bradford Hill analysis" for each cancer type, the gold-standard method for "determin[ing] whether an association truly reflects a causal relationship or is spurious." *Milward*, 639 F.3d at 18; *Reference Manual on Scientific Evidence* (Federal Judicial Center, 3d. ed. 2011) ("*Reference Manual*") at 598-99 (stating that the Bradford Hill criteria are used "to determine whether that association reflects a true causal relationship"); *see, e.g.*, MDL.Dkt.6171-9 (McTiernan) at 201-05

(bladder); 220-26 (esophageal); 235-39 (liver); 252-58 (pancreatic); 281-87 (stomach); MDL.Dkt.6179-6 (Moorman) at 110-18 (bladder); 134-42 (pancreatic); 161-71 (liver); 188-99 (esophageal); 221-31 (stomach).[7] This analysis, for which "no algorithm exists" and which again requires the use of "judgment," involves evaluating the "strength of the association," "consistency," "specificity," "temporality," "dose response," "plausibility," "coherence," "experiment[al results]," and "analogy." *E.g.*, MDL.Dkt.6171-9 at 93-94 (McTiernan).[8] After performing that analysis, the experts concluded that "ranitidine can cause [the five designated] cancer[s]." *E.g.*, *id.* at 207.

After *Daubert* briefing had concluded and oral argument had occurred on Defendants' *Daubert* motions, and just days before oral argument on Plaintiffs' *Daubert* motions, a new study linking ranitidine and cancer was published. MDL.Dkt.6061-6 (Wang). This "real-world observational study" encompassed a patient population of "over 99% of Taiwan's population." *Id.* at 2-3. The purpose of the study was to "assess the relationship between the cumulative individual cancer incidence and long-term ranitidine use." *Id.* at 2; *see also id.* ("We conducted a population-based study to explore ranitidine use and cancer emergence over time."); *id.* at 3 ("[W]e aimed to conduct a large-scale, long-term follow-up cohort study to

[7] Drs. Le, Michaels, and Salmon similarly include Bradford Hill analyses.

[8] All experts used these same criteria.

investigate ranitidine use and subsequent emergence of cancer over time in a real-life setting.").

The results were striking: "long-term ranitidine use [was] associated with a higher likelihood of cancer development in ranitidine users." *Id.* at 13. A patient who took ranitidine had a 10% higher risk of developing any cancer, a 6% higher risk of developing bladder cancer, a 35% higher risk of developing pancreatic cancer, a 26% higher risk of developing stomach cancer, a 27% higher risk of developing esophageal cancer, and a 22% higher risk of developing liver cancer. *Id.* at 8 (Fig. 2) (showing statistically significant hazard ratios of 1.10, 1.35, 1.26, and 1.22 for all cancer, pancreatic cancer, gastric cancer, and liver cancer, respectively, and hazard ratios of 1.27 and 1.06 for esophageal and bladder cancer). The study "strongly support[ed] the pathogenic role of NDMA contamination, given that long-term ranitidine use is associated with a higher likelihood of liver cancer development in ranitidine users." *Id.* at 2. With respect to gastric and pancreatic cancers, the study "revealed the association of ranitidine usage with [those] cancers." *Id.* at 13.

Given the importance of this new study, Appellants moved to supplement their experts' reports to address it. Defendants agreed, and both sides stipulated to limited supplemental reports, but "no further depositions of the[] experts." MDL.Dkt.6047 at 1. But the district court intervened, rejected the parties' agreement, and ordered twelve hours of depositions against the five plaintiff experts,

but allowed Defendants to select only one of their experts to be deposed. MDL.Dkt.6056 at 2. The parties likewise agreed that no additional briefing on this additional study would be necessary, but again, the district court intervened, ordering supplemental briefs. MDL.Dkt.6083.

The district court ultimately granted Defendants' *Daubert* motions in full, holding that none of the experts could testify. MDL.Dkt.6120 at 337. Despite the unusual length of the district court's *Daubert* opinion, the overall reasoning can be succinctly stated: the district court barred the experts from testifying that Zantac can cause cancer because (in the district court's view) "no scientist outside this litigation [has] concluded ranitidine causes cancer." *Id.* at 7.[9] That focus on conclusions animated the 334 pages that followed.

First, in deciding whether to treat this case as a "category 1" case under *McClain*, for which no extensive *Daubert* analysis is necessary, the district court repeated that the scientific community has not yet unanimously identified ranitidine itself as causing cancer—even though the scientific community has recognized that NDMA causes cancer. *Id.* at 25-28. Second, when addressing the experts'

[9] This statement is legally misguided and factually misleading. There are numerous statements supporting causation in the medical literature, for example, "[t]he conclusive results of our study after gathering data emphasize that consuming high levels of NDMA due to ranitidine use is linked to liver cancer development" and that "the risk of carcinogenic effects on the liver" observed was "caused by increasingly heavier ranitidine usage." MDL.Dkt.6061-6 at 14 (Wang).

methodologies, the district court credited as a "factor in favor of exclusion" Defendants' argument that no study "concluded that there was evidence of an association—let alone causation—between ranitidine and cancer." *Id.* at 171. Indeed, the district court held that this purported "lack of independent scientific support is a valid ground for the Court to grant the Defendants' Epidemiology Motion because it is a valid ground for the Court to question the reliability of the Plaintiffs' experts' methodologies." *Id.* at 177.

Having placed its thumb on the scale based on the experts' *conclusions*, the district court undertook an independent evaluation of the underlying studies to determine *its own view* of whether they supported causation. In doing so, the district court had no choice but to gerrymander what counts as reliable evidence. For example, although many epidemiological studies demonstrated an association between ranitidine use and cancer—often with statistically significant results—the court discounted all those studies unless they stated that ranitidine *causes* cancer, something such studies never do. *E.g.*, *id.* at 173. Although numerous studies showed that patients who took ranitidine developed cancer at higher rates than patients who did not take ranitidine, the district court held that a reliable scientist could not rely on those results. Instead, in the district court's view, only results comparing ranitidine users to users of other antacid medications—and indeed antacid medications in the exact same drug class—could reasonably be relied upon.

E.g., *id.* at 257. Although epidemiologists (and the FDA) regularly rely upon results that are not statistically significant, the district court faulted the experts for doing so. *E.g.*, *id.* at 176-77. Although ranitidine undisputedly contains NDMA, the district court held that no reasonable expert could rely on studies about NDMA when forming an opinion about ranitidine. *E.g.*, *id.* at 313. Although the experts provided numerous reasons for crediting some studies and discounting others, the district court decided which were the real reasons, and then decided those reasons were (in the district court's view) illegitimate. *E.g.*, *id.* at 191.

In the end, the district court concluded that only one kind of study result was valid evidence of causation: a study comparing users of ranitidine to users of H2 blockers that demonstrated a statistically significant result and inferred that ranitidine can cause cancer. *See id.* at 192-93. And when one of those studies appeared, with striking results—the Wang study—the district court held that even that was not enough. *Id.* at 283-96.

The district court held that the experts failed to employ any of the three primary methodologies recognized by this Circuit, namely background risk, dose response, and epidemiology. *Id.* at 321. The court acknowledged that the experts used these methodologies. *Id.* at 161 (epidemiology), 300 (dose-response), 321 (background risk). But the court evaluated the underlying studies and determined, in its view, that they were unreliable. The Court repeatedly made clear that this

grounded its decision. *Id.* at 321 ("Because the Plaintiffs lack primary evidence, under Eleventh Circuit case law, all of the Plaintiffs' general causation experts are stricken."); *id.* ("Given the Plaintiffs' lack of primary evidence, the Court does not need to analyze the remainder of the Plaintiffs' secondary evidence").

At every turn, the district court went out of its way to (try to) insulate its opinion from appellate review. For example, rather than identifying one or two reasons for excluding an expert, the district court identified nine or ten—including a catch-all "evidence in the totality" to the extent "the Court is wrong as to some subset of the Court's prior nine conclusions." *Id.* at 264; *see also* 283 ("[E]ven if the Court is wrong as to some subset of the Court's prior eight conclusions, the Court's analysis of Dr. Moorman's methodology is in the totality."). Rather than rest on its (wrong) decision that Plaintiffs had somehow waived reliance on "background risk," the district court provided no less than three rapid-fire alternative holdings without any analysis at all. *Id.* at 321 ("Plaintiffs' experts do not offer background-risk-based opinions ... In the alternative … Also in the alternative ...."). The list goes on. The district court protests too much in claiming that its order exceeds "300 pages because the Court has endeavored to carefully explain each

reason why the Plaintiffs' experts have utilized unreliable methodologies." *Id.* at 7.[10] The true reason is apparent.

STANDARD OF REVIEW

This Court reviews a district court's order on a motion to dismiss *de novo*. *United States ex rel. Sanchez v. Lymphatx, Inc.*, 596 F.3d 1300, 1302 (11th Cir. 2010).

Daubert orders are reviewed for abuse of discretion. *United States v. Brown*, 415 F.3d 1257, 1266 (11th Cir. 2005). Although the standard is deferential, "review under an abuse of discretion standard does entail review, and granting considerable leeway is not the same thing as abdicating appellate responsibility." *Id.* If the district court makes "an error of law," that error "is by definition an abuse of discretion." *In re Lipitor (Atorvastatitn Calcium) Mktg., Sales Pracs. & Prods. Liab. Litig. (No. II)*, 892 F.3d 624, 632 (4th Cir. 2018); *Brown*, 415 F.3d at 1266. And "[a]n abuse of discretion occurs when under *Daubert* the admissibility bar is too high." *Allison*, 184 F.3d at 1321.

SUMMARY OF ARGUMENT

As argued in the Generic-Only brief, the district court lacked diversity jurisdiction and erred in its preemption rulings.

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[10] The district court's order addresses the Wang study separately, at the end, suggesting the court had already written the order before the Wang study was published (and so before the hearing).

The district court also erred in excluding Appellants' experts under *Daubert*. First, because NDMA is widely recognized to cause cancer and ranitidine degrades into NDMA, this is a *McClain* category 1 case. 401 F.3d at 1246. The district court erred by focusing on ranitidine, not the toxin at issue (NDMA). Worse, the district court used its conclusion that ranitidine's carcinogenicity is not generally accepted *both* to place this case into *McClain* category 2, *and* to hold that it failed within that category.

Second, the district court misapplied this Court's primary methodologies test. This Court requires general causation experts to utilize a methodology based on epidemiology, dose-response, or background risk. The experts did all three. The district court erroneously held otherwise by weighing the science for itself, finding that the *underlying studies* did not constitute reliable "primary evidence."

Third, the district court focused on conclusions, not methodology. It emphasized that the scientific community has not yet accepted the conclusion that ranitidine can cause cancer, but that is not a methodological flaw. Next, it fashioned a checklist for reliable studies. To be reliable, a study must show a statistically significant positive association; address ranitidine only (not NDMA); state expressly that ranitidine causes cancer; and employ an active-comparator study design. It then held that no study met these criteria, but its checklist does not match the scientific community's or this Court's.

Fourth, the district court excluded individual experts for insubstantial reasons, and in doing so made clear its intention to insulate its order from appellate review.

After deciding *Daubert*, the district court concluded that it had decided, as a preclusive matter, the element of general causation for the entire MDL. Thus, it granted judgment in the class cases, in favor of non-moving parties, and in later-filed cases. This violated due process and the federal rules.

Last, the district court erroneously predicted that 35 jurisdictions would bar consumers of generic ranitidine from recovering against the Brand Defendants that crafted the label they relied upon. This holding misapplied fundamental *Erie* prediction principles. This Court should certify the question to state courts or vacate. The district court dismissed claims under California and Massachusetts law for lack of personal jurisdiction. That was erroneous. If it were correct, deciding the merits was *ultra vires* for those claims, requiring vacatur.

ARGUMENT

I. The District Court Lacked Diversity Jurisdiction And Its Rule 12 Preemption Dismissals Were Erroneous.

A. The District Court Lacked Subject-Matter Jurisdiction Because the Parties Are Not Completely Diverse.

For the reasons argued in the Generic-Only Appellants' opening brief, the district court below lacked diversity jurisdiction, and its orders should be vacated.

B. The District Court Erred in Holding That Impossibility Preemption Bars State-Law Claims in the MPIC That Parallel Federal Law.

All Plaintiffs argued that the claims in the MPIC survived preemption against every category of Defendant to the extent they paralleled federal law. Simply put, federal law prohibited any Defendant from selling ranitidine, and so federal law does not operate as a shield for their conduct, which violated state *and* federal law. The district court rejected that argument. *See* MDL.Dkt.2512 (Generic Preemption Order), 2513 (Distributor, Retailer, and Pharmacy Preemption Order), 2532 (Brand Preemption Order). As argued in the Generic-Only Appellants' opening brief, the parallel misbranding argument is sound, and the district court's dismissal was erroneous. Appellants incorporate the arguments in that brief by reference, which apply with full force to the other Defendants too.

C. The FDCA Does Not Preempt the Amended Claims Because They Rest on State Law Requirements That Defendants Could Have Fulfilled.

The district court dismissed all claims against the Generic Defendants in the AMPIC on preemption grounds, MDL.Dkt.3750, and Count V against the Brand Defendants, MDL.Dkt.3715. Appellants incorporate the arguments made in the Generic-Only opening brief, both as to the Generic Defendants, and, with respect to Count V, the Brand Defendants as well.

II. The District Court Erred In Granting Summary Judgment.

A. The *Daubert* Legal Standard

"In analyzing [an] experts' testimony" under *Daubert*, "toxic tort cases usually come in two broad categories." *McClain*, 401 F.3d at 1239. The first is "cases in which the medical community generally recognizes the toxicity of the drug or chemical at issue." *Id*. For this category, the district court "need not undertake an extensive *Daubert* analysis" as to general causation. *Id*. at 1239; *see also Chapman*, 766 F.3d at 1314 (this category "eliminate[s] the *Daubert* analysis of" the plaintiffs' general causation experts).[11] The second *McClain* category consists of "cases in which the medical community does not generally recognize the agent as both toxic and causing the injury plaintiff alleges." 401 F.3d at 1239. For cases in this category, "the *Daubert* analysis covers ... the general question of whether the drug or chemical can cause the harm plaintiff alleges." *Id.*; *Chapman*, 766 F.3d at 1303.

Rule 702 and *Daubert* provide for "the liberal admission of expert testimony." *Johnson v. Mead Johnson & Co.*, 754 F.3d 557, 562 (8th Cir. 2014). "After *Daubert*, 'the rejection of expert testimony is the exception rather than the rule.'" *Moore v.*

[11] In *McClain* Category 1 cases, the *Daubert* analysis proceeds immediately to specific causation *i.e.*, "was plaintiff exposed to the toxin, was plaintiff exposed to enough of the toxin to cause the alleged injury, and did the toxin in fact cause the injury." *McClain*, 401 F.3d at 1239; *see Chapman*, 766 F.3d at 1303 n.6.

Intuitive Surgical, Inc., 995 F.3d 839, 850 (11th Cir. 2021) (citation omitted). Courts must not "improperly use the admissibility criteria to supplant a plaintiff's right to a jury trial," *id.*, because "cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof"—not exclusion—"are the traditional and appropriate means of attacking shaky but admissible evidence." *Daubert v. Merrell Dow Pharms.*, 509 U.S. 579, 596 (1993).

When reviewing expert testimony, "[i]t is not the role of the district court to make ultimate conclusions as to the persuasiveness of the proffered evidence." *Quiet Tech.*, 326 F.3d at 1341. "[S]cientific knowledge is far afield from the normal expertise of judges and ... they should proceed with caution lest they exceed their grasp." *Allison*, 184 F.3d at 1310. The district court may not evaluate "the persuasiveness of competing scientific studies." *Quiet-Tech*, 326 F.3d at 1341; *accord Schultz v. Akzo Nobel Paints, LLC*, 721 F.3d 426, 432-33 (7th Cir. 2013) (Where two studies conflict, Rule 702 does not "permit[] the district court to choose between those two studies at the gatekeeping stage."); *Hardeman v. Monsanto Co.*, 997 F.3d 941, 964 (9th Cir. 2021) (expert testimony was properly admitted despite reliance on competing studies). The district court may not "determine which of several competing scientific theories has the best provenance." *Milward*, 639 F.3d at 15. And the district court may not "[take] sides on questions that are currently the focus of extensive scientific research and debate." *Id.* at 22.

Instead, the district court must "meticulously focus on the expert's principles and methodology, and not on the conclusions that they generate." *Chapman* 766 F.3d at 1305. The party proffering the expert need not show that the "testimony ... is scientifically correct" to the district court's satisfaction, but merely that the expert's methods are "reliable." *Allison*, 184 F.3d at 1312. The district court decides only "whether the expert 'employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.'" *Rider v. Sandoz Pharms. Corp.*, 295 F.3d 1194, 1197 (11th Cir. 2002) (citation omitted). "So long as an expert's scientific testimony rests upon '"good grounds," based on what is known,' it should be tested by the adversarial process, rather than excluded for fear that jurors will not be able to handle the scientific complexities." *Milward*, 639 F.3d at 15 (citations omitted).

B. The District Court Misapplied *McClain's* Two-Part *Daubert* Taxonomy.

McClain teaches that when the molecule at issue is generally recognized as causing a certain disease, no extensive *Daubert* analysis is necessary. *McClain*, 401 F.3d at 1239; *Chapman*, 766 F.3d at 1303. Where the molecule at issue is *not* generally recognized as causing a certain disease, the district court conducts a traditional *Daubert* analysis to determine whether the experts' methodologies are reliable. *McClain*, 401 F.3d at 1239; *Chapman*, 766 F.3d at 1303.

Here the district court bungled both parts of this analysis. It failed to recognize that this is a Category 1 case, wrongly analyzing the question of whether ranitidine is generally recognized as a carcinogen rather than whether NDMA is. Having made that level-of-generality error, it then proceeded to deem the fact that ranitidine is not generally recognized as a carcinogen (even though NDMA is) as an independent reason to exclude the experts in its Category 2 analysis. This was doubly wrong and requires reversal.

1. This case is in category one under *McClain*.

The district court committed a pure error of law by mis-categorizing this case under *McClain*. *Every* ranitidine pill degrades into NDMA as a matter of basic chemistry. The NDMA found in ranitidine is chemically identical to NDMA found everywhere else. The medical community generally recognizes that NDMA causes cancer. *See supra* notes 4-5. In fact, Dr. Errol Zeiger submitted an expert report with the opinion that "The carcinogenicity and mutagenicity of N-nitrosodimethylamine (NDMA) has been well-established among the scientific and regulatory communities in the US and internationally for more than 50 years. NDMA is generally accepted by the scientific and regulatory communities in the US and internationally as genotoxic and carcinogenic." MDL.Dkt.6185-8 at 3. Defendants *did not even move to exclude Dr. Zeiger's opinions*. *See generally* MDL.Dkt.5736.

When Appellants in this MDL ingested ranitidine, therefore, there is no dispute that they ingested a substance "generally recogniz[ed]" to "cause the injury" alleged in this ligation. *Chapman*, 766 F.3d at 1303. That makes this a Category 1 case under *McClain*. *See* 401 F.3d at 1239. The Valsartan court reached this exact conclusion—although not bound by *McClain's* taxonomy—in holding that NDMA's carcinogenic nature was enough to presumptively establish general causation. MDL.Dkt.6182 at 224.

In reaching the opposite conclusion, the district court made a number of errors. *First*, the district court held that this is not a Category 1 cases because *ranitidine* is not "generally recognized by the scientific community as a carcinogen capable of causing cancer." MDL.Dkt.6120 at 26; *id.* at 178 ("[T]he product at issue in this MDL is ranitidine, not NDMA."). This is a simple logic error. All ranitidine contains NDMA; NDMA is a recognized carcinogen; therefore, users of ranitidine consume a known carcinogen. A contrary conclusion would require holding that only when consuming a 100% pure substance—and nothing else—that is known to cause a disease does a case fall within *McClain* Category 1. That is not the law, as *McClain* makes clear.

For example, *McClain* holds that a case alleging that "too much alcohol causes cirrhosis of the liver" would be in Category 1. *McClain*, 401 F.3d at 1239 n.5. But as with NDMA, alcohol can be delivered into a person's body in a variety of ways—

beer, wine, cocktails, and so on. Every alcoholic drink contains ingredients aside from alcohol—hops, water, grapes. As with NDMA, only one "component of" those delivery vehicles, MDL.Dkt.6120 at 26—the alcohol—causes cirrhosis. Where a plaintiff alleged cirrhosis from drinking too much Miller Lite (or martinis or chardonnays), it would be no answer to say that the scientific community has not recognized the cirrhosis-producing potential of Miller Lite, because it is simply the delivery vehicles of ethyl alcohol.[12] It is enough that the cirrhosis-producing potential of that toxic ingredient has been recognized. The same is true for ranitidine, NDMA, and cancer.[13]

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[12] The same is true for other examples in *McClain*. Nobody thinks vermiculite causes mesothelioma. Asbestos does. But because 70% of vermiculite used for insulation came from a mine with asbestos deposits, the Environmental Protection Agency warns consumers that if they "have vermiculite insulation in [their] homes, [they] should assume this material may be contaminated with asbestos." *Protect Your Family from Asbestos-Contaminated Vermiculite Insulation*, EPA (updated June 5, 2023), https://www.epa.gov/asbestos/protect-your-family-asbestos-contaminated-vermiculite-insulation. If such a consumer contracted mesothelioma, an expert could obviously opine on the causal link between that disease and asbestos. This case is even starker. While only 70% of vermiculite contains asbestos, *all* ranitidine degrades into NDMA. Take other Category 1 exposures. Even with no evidence about a *particular* brand of cigarettes, the cigarette smoke/heart disease connection is Category 1. Arsenic remains a Category 1 substance despite the numerous ways that mystery writers have dreamt up to deliver it.

[13] In the district court's view, since "the product at issue in this MDL is ranitidine, not NDMA," Plaintiffs were somehow wrong to use the phrases "NDMA in ranitidine" and "NDMA causes cancer" in their *Daubert* briefs. MDL.Dkt.6120 at 178-79. But as the district court acknowledged, NDMA is "the mechanistic theory" *by which* ranitidine causes cancer. *Id.* It makes sense, therefore, to refer to "NDMA

Second, the district court held that "the facts in this MDL are not distinguishable from" *Chapman*. *Id.* at 28. But *Chapman* actually confirms the district court's error. In *Chapman*, the injury at issue was myelopathy, and the substance at issue was a calcium-zinc compound delivered to the body via a denture cream called "Fixodent." 766 F.3d at 1300-02. When determining whether the case was in Category 1, this Court did not look *only* at whether it was generally accepted that *Fixodent* caused myelopathy (as the district court did here). Instead, the court looked at whether it was "generally accepted by the medical community that zinc causes [myelopathy]." *Chapman*, 766 F.3d at 1314. By framing the question as about zinc, rather than Fixodent, *Chapman* makes clear that the relevant *McClain*-categorization question concerns the toxin rather than the delivery vehicle. Here, that means the question is whether NDMA is generally recognized as causing cancer. And the answer is a resounding "yes."[14]

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in ranitidine" and argue that "NDMA causes cancer"—just as it would make sense to refer to the "alcohol in beer" and say "alcohol causes cirrhosis" in a case where the "product at issue" was beer. *McClain*, 401 F.3d at 1239 n.5.

[14] The district court relied on the trial-court opinion in *Chapman*. *See* MDL.Dkt.6120 at 26. That opinion is not binding, but also *did not need to answer* the product-or-toxin question because "there [wa]s no reliable basis to conclude *either* Fixodent *or* zinc can cause [myelopathy]." *In re Denture Cream Prods. Liab. Lit.*, 795 F. Supp. 2d 1345, 1350 (S.D. Fla. 2011). The trial-level opinion examined *both* zinc and Fixodent. *Id.* at 1350 n.8 (holding that "the alleged association between the zinc in Fixodent and copper-deficiency myelopathy does not have [general acceptance]").

Third, the district court held that, because NDMA is "found in trace amounts in air, water, and food," Plaintiffs' position is that "no plaintiff in the Eleventh Circuit need produce evidence for" the proposition that air, water, and food cause cancer. MDL.Dkt.6120 at 29. This same *reductio ad absurdum* argument could apply to every *McClain* category 1 substance. For example, a 70-year-old plaintiff could allege that he developed lung cancer because he once sneaked a pack of cigarettes in the eighth grade. The answer to this argument is the distinction between general and specific causation. If a plaintiff consumed meat contaminated with NDMA (or one cigarette, 30 years ago), the court would not conduct a *Daubert* analysis on general causation. *See McClain*, 401 F.3d at 1239. But that hardly means no additional evidence would be required. To establish *specific* causation, the plaintiff would need to show that the meat (or cigarette) exposed him to "enough of the toxin" to cause his cancer and that "the toxin" did "in fact cause the injury" rather than something else. *Chapman*, 766 F.3d at 1303 n.6 (quoting *McClain*, 401 F.3d at 1239) (noting that these are specific-causation questions). NDMA in air, water, and foods is found in only "trace amounts," MDL.Dkt.6120 at 28, which would make such specific-causation evidence impossible to muster.[15]

[15] The district court nods toward the issue of dose, pointing out that the *Chapman* district court disputed whether "**[o]ne can ingest enough zinc from Fixodent to place the body in a negative copper balance**," a prerequisite for myelopathy. MDL.Dkt.6120 at 27. But the *Chapman* court did *not* make this statement when

Finally, the district court placed this case in Category 2 because its "detailed analysis" showed that the experts' opinions were "no[t] reliable" under *Daubert*. *Id.* at 29. This is an obvious order-of-operations error. The first question is whether the substance is "generally recognize[d]" to "caus[e] the injury plaintiff alleges." *Chapman*, 766 F.3d at 1303. When, as here, that is true the court does *not* perform a "detailed analysis" of the experts' opinions. *See Chapman*, 766 F.3d at 1303 (In Category 1 cases, judges "need not undertake an extensive *Daubert* analysis on the general toxicity question" but instead should move on to "specific causation."). In holding that this "detailed analysis" determined the *categorization* under *McClain*, the district court was either confused about how *McClain* works, or perhaps was attempting to insulate its opinion from appellate review.

2. The district court wrongly conflated the two *McClain* categories.

This analytical confusion infected the district court's *McClain* Category 2 analysis. When evaluating whether the experts employed a generally reliable methodology, the district court repeatedly discounted their methodology on the grounds that the experts' conclusions—that Zantac can cause cancer—were not

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evaluating the *McClain* categorization issue. Rather, it was evaluating the experts' opinions about biological plausibility. 795 F. Supp. 2d at 1357-58. The reason is obvious from the case law: for substances that are generally accepted to cause a certain disease, dose is a question for specific causation, not general causation. *See Chapman,* 765 F.3d at 1296 n.6 (holding that the question of whether the plaintiff was "exposed to enough of the toxin to cause the alleged injury" is a question about "individual causation").

generally accepted in the medical community. *See, e.g.*, MDL.Dkt.6120 at 6, 169, 177, 180, 228, 250, 259, 281, 299. To take a striking example, the district court acknowledged that the Wang study "could be interpreted as [itself] concluding ranitidine *causes* liver cancer." *Id.* at 289 (emphasis added). Nevertheless, the district court noted that there is "no *widespread* acceptance of the Plaintiffs' experts' general causation opinions." *Id.* (emphasis added) And for *that reason*, the district court repeatedly put a thumb on the scales against the experts when evaluating their *methodologies*. *See, e.g.*, *id.* at 180.

This analysis conflated the two *McClain* categories. When a case falls into *McClain* Category 1—*i.e.*, when it is generally accepted that a substance causes a certain disease—the experts sail through *Daubert* without further analysis. *Chapman*, 766 F.3d at 1303; *McClain*, 401 F.3d at 1239. But when it is *not* generally accepted that a substance causes a certain disease, that simply means the case falls into *McClain* Category 2, not that the experts' opinions should be excluded. If the district court's reasoning were right, there would be no daylight between the two *McClain* categories, since the same feature that placed a case in Category 2 would also support excluding the expert's opinion. By requiring evidence of general acceptance of *conclusions* when evaluating the experts' *methodologies*, the district court improperly mixed and matched features between the two categories. Under the district court's rule, even when some independent publications agree with the

experts' conclusions, the absence of *widespread* agreement is reason to look suspiciously at the experts' methodology. That is not the law.

C. The District Court Erred in Applying this Court's Primary Methodology Test.

For two reasons, the district court erred when it held that the experts did not "rel[y] upon any form of reliable primary evidence in support of their general causation opinions." MDL.Dkt.6120 at 321. First, the district court's framing of the relevant inquiry is wrong. Second, the experts here relied on not just *one* form of reliable primary evidence, but all three forms.

1. The district court wrongly used the primary methodology requirement to conduct its own evaluation of the evidence underpinning each methodology.

First, the district court mistook this Court's directive that *an expert* must rely on at least one primary methodology as a license to weigh, rank, and decide for itself how the primary methodological evidence cuts. Nothing in this Court's jurisprudence treating primary methodologies as indispensable gives a district court the "obligation or the authority to become amateur scientists." *In re Joint E. & S. Dist. Asbestos Litig.*, 52 F.3d 1124, 1137 (2d Cir. 1995) (quoting *Daubert*, 509 U.S. at 601 (Rehnquist, C.J., concurring in part and dissenting in part)). If an expert testifies that a substance causes a certain disease, but his only evidence is animal studies, the expert must be excluded because he has not relied upon at least one primary methodology. *See Chapman*, 766 F.3d at 1308.

These experts did not do that. Instead, each of the experts painstakingly evaluated the "epidemiology" both as to NDMA and ranitidine.[16] In analyzing each study, each expert confirmed that the cancer rates for those taking ranitidine and exposed to NDMA exceeded the "background risk" for cancer in the population generally (non-users). And each expert catalogued data demonstrating dose-response for both NDMA and ranitidine as part of their Bradford Hill analysis, *i.e.*, data showing that when patients were exposed to more NDMA and ranitidine, their cancer rates increased even more.[17] In other words, they checked all three of the primary-methodology boxes—a fact the district court acknowledged. *See* MDL.Dkt.6120 at 161 ("Five of the Plaintiffs' experts rely upon epidemiological studies"); *id.* at 300 ("[T]he topic of dose-response relationship received ... discussion in the expert reports."); *id.* at 321 (acknowledging "references to background risk in the Plaintiffs' experts' reports").

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[16] *E.g.*, MDL.Dkt.6185-5 at 54-104 (Salmon) (NDMA epidemiology) 143-65 (ranitidine epidemiology); MDL.Dkt.6171-9 at 101-84 (McTiernan); MDL.Dkt.6179-6 at 63-88 (Moorman).

[17] *E.g.*, MDL.Dkt.6171-9 at 205 (McTiernan) (dose-response for bladder cancer), 224 (esophageal), 238 (liver), 256 (pancreas), 284-85 (stomach); MDL.Dkt.6179-6 at 49 (Moorman) ("Dose-response analyses are an important component of making a causal assessment and my review of relevant studies (both ranitidine studies and those of other sources of NDMA exposure) included an evaluation of trends of increasing cancer risk with increasing exposure."); MDL.Dkt.6061-4 at 4 (Moorman Supp.) ("The HRs for liver cancer showed increasing risk with increasing dose of ranitidine ....").

The district court grounded its decision not on the experts' failure to use a primary methodology, but on its *disagreement* with the conclusions. That is error because a district court may not evaluate "the persuasiveness of competing scientific studies." *Quiet-Tech*, 326 F.3d at 1341. The expert's overall *methodology* must be reliable, and the expert must rely on at least one primary methodology. But the district court may not atomistically examine the studies underlying each of the primary methodologies, declare them invalid, and *on that basis* exclude the expert under the primary-methodology rule. That would amount to "the district court impermissibly ma[king] a number of independent scientific conclusions." *In re Joint*, 52 F.3d at 1137.

That is exactly what the district court did. The district court first reviewed the evidence of background risk, epidemiology, and dose response—over more than 150 pages. *See* MDL.Dkt.6120 at 161-298 (epidemiology); 299-318 (dose-response); 319-21 (background risk). The district court deemed that evidence unreliable, and on that basis excluded the experts. *See id.* at 321 ("Because Plaintiffs lack primary evidence ... all of the Plaintiffs' general causation experts are stricken."); *id.* at 321-22 ("Given the Plaintiffs' lack of primary evidence, the Court does not need to analyze the remainder of the Plaintiffs' secondary evidence.").

The facts in *Chapman* illustrate why this was error. There, the experts admitted they relied on "no controlled population-based epidemiologic studies" *at*

all. *Chapman*, 766 F.3d at 1307 n.10. They testified that they *had no* evidence of "dose response" *at all*. *Id.* at 1307 n.9 (quoting expert admission). And they testified that they *had no* evidence about "background risk" *at all*. *Id.* at 1307 n.11 (quoting expert admission that they had no idea about the background risk of the relevant disease). That was sufficient grounds to exclude *those* experts, but here the opposite is true: the experts each testified that they *had* relied on evidence based on epidemiology, dose response, and background risk. *See supra* notes 16-17. That should have been the end of the primary-methodology-test analysis.

2. The experts employed each primary methodology reliably.

a. The experts reliably employed studies showing background risk.

First, the experts certainly had reliable evidence of background risk, which simply means the risk "members of the general public have of suffering the disease or injury that plaintiff alleges without exposure to the drug or chemical in question." *McClain*, 401 F.3d at 1243. The test for whether an expert has employed "a reliable methodology [based on] background risk" is straightforward: a showing "that taking [the substance in question] increases the risk of [the relevant disease] beyond the usual incidence of" the disease. *Id.* at 1243-44.

The experts "base[d] [their] opinion[s]" on exactly this kind of evidence, namely "the elevated risk estimates ... for use of ranitidine." MDL.Dkt.6171-9 at 16 (McTiernan). Dr. Moorman discussed ranitidine-user-versus-non-user comparisons

for each cancer, which capture the increased risk above the background rate. *E.g.*, MDL.Dkt.6179-6 at 65 (discussing bladder studies "comparing ranitidine users to non-users" which measure "the cancer risk associated with ranitidine generally"). There is no dispute that the experts relied on evidence showing "the usual incidence of" cancer—and demonstrating that Zantac and NDMA increased that incidence rate. For example, the Wang study reported the rate of liver cancer for "untreated" patients as 1.1% (the background risk) and that the rate for patients treated with ranitidine as 1.3%—a 20% risk increase over the background. MDL.Dkt.6061-6 at 8;[18] *McClain*, 401 F.3d at 1244. That is all that is required to reliably apply the background risk methodology under *McClain*. Perhaps for this reason, Defendants *never argued* that the experts failed to rely on background risk—or that they should be excluded for that reason. *See generally* MDL.Dkt.5736.

Ignoring Defendants' waiver, the district court first held that *Plaintiffs* had somehow waived reliance on the background risk methodology by not highlighting

[18] There are numerous other examples like this. MDL.Dkt.6061-6 at 9 (Wang) (statistically significant increased risk compared to background rate for liver, gastric, pancreas, lung, and overall cancer); MDL.Dkt.6185-31 at 5 (Cardwell) ("using more than 1,095 ranitidine DDDs, the fully adjusted OR [for bladder cancer] was 1.43 (95% CI 1.05-1.94), compared with no use"); MDL.Dkt.6185-15 at 6 (Liu) (1.43 gastric cancer compared to background rate), MDL.Dkt.6187-5 at 4 (Habel) (increased risk of 2.42 the background rate for esophagus/stomach, and 2.6 for pancreas); MDL.Dkt.6187-9 at 2 (Kantor) (liver); MDL.Dkt.6187-18 at 6 (McDowell) (pancreatic).

it in their response brief. MDL.Dkt.6120 at 319-21. But a non-moving party has has no burden to respond to arguments that are never made. Nevertheless, the district court mistakenly held that the Defendants made this argument "by implication" simply by asking for "summary judgment." *Id.* at 320. This was basic procedural error. An opponent only has an obligation to point to admissible evidence on a disputed point *after* the moving party shows that there is no triable issue of fact. *Celotex Corp. v. Catrett*, 477 U.S. 317, 325 (1986); 10A Charles Alan Wright & Arthur R. Miller, Fed. Prac. & Proc. §2727.1 (4th ed.) ("A party moving for summary judgment has the burden of demonstrating to the court that [it is] entitled to judgment as a matter of law."). It makes no sense to suggest that the failure of *both sides* to brief an issue in detail entitles a movant to summary judgment.

The district court examined the experts' reports *sua sponte,* determining that "the Plaintiffs' experts do not offer background-risk-based opinions," that any such opinions "do not meet any of the *Daubert* factors," and that any such methodology was not "reliable." MDL.Dkt.6120 at 321.[19] This drive-by alternative-holding has no analysis at all and cannot support exclusion (much less on three grounds). The district court never explained why the experts' analysis of background risk was unreliable or why background risk was not indeed a basis for their opinions. Nor

[19] Once again, the district court attempted to insulate its opinion from review, hoping that alternative holdings (rather than sound legal analysis) could support affirmance.

could there be any such explanation: patients who consumed Zantac (and NDMA) developed cancer at higher rates than patients in the general population who had not consumed those substances. *See supra* note 18. That is exactly what this Circuit's "primary methodology" of "background risk" requires. *McClain*, 401 F.3d at 1244.

b. The experts reliably employed epidemiology studies.

The experts also reliably employed epidemiology studies in support of their opinions. As the district court acknowledged, "clinical trials are often unavailable in toxic tort cases because it is unethical to randomly assign a human a potentially harmful dose of" NDMA. MDL.Dkt.6120 at 162. To determine whether a substance causes cancer, experts rely on "observational studies" that compare cancer rates in patients exposed to ranitidine and NDMA to unexposed patients. The experts pointed to multiple studies, for each cancer, showing that patients exposed to ranitidine developed cancer at higher rates than unexposed patients. *E.g.*, MDL.Dkt.6179-6 at 108 (Moorman) (describing "relative risks" for bladder cancer ranging from "1.11 to 1.56 for ranitidine use"). The experts also pointed to multiple studies for each cancer showing that patients exposed to NDMA developed cancer at higher rates than unexposed patients. *E.g.*, *id.* ("The relative risks [were] ... 1.2 to 2.82 for occupational exposure to NDMA, 1.12 to 2.16 for dietary NDMA exposure, and 1.2 to 1.47 in the meta-analysis and cohort study of processed meat in relation to bladder cancer.").

These epidemiology results are entirely consistent with the basic facts of this case: the scientific community acknowledges that NDMA is a human carcinogen, and Defendants acknowledge that every ranitidine pill degrades into NDMA. One would therefore expect that patients exposed to ranitidine would develop cancer at higher rates. That expectation was borne out in the studies on which the experts rely.[20] When a substance containing a known carcinogen is associated with higher cancer rates, epidemiologists like the experts here can take account of that. Their reliance on epidemiology was therefore reliable under *Daubert*.

c. The experts reliably employed studies showing dose-response.

Finally, the experts reliably employed evidence showing dose-response. A "positive dose-response relationship" means that "an increase in how much or how long a person is exposed to the substance would increase that persons' risk of developing the disease." MDL.Dkt.6120 at 300. An expert need not "give precise numbers about a dose-response relationship." *Williams v. Mosaic Fertilizer, LLC*,

[20] Not every study shows an increased risk from ranitidine, but that, too, is unsurprising. Given the measurement difficulties when randomized controlled trials cannot be employed, not every study will show a result, even for well-established carcinogens. Kenneth J. Rothman, et al., *supra* at 65; *Reference Manual* at 604 ("[I]nconsistent results do not necessarily rule out a causal nexus."). And when there are conflicting study results, the district court may not "[take] sides on questions that are currently the focus of extensive scientific research and debate." *Milward*, 639 F.3d at 22.

889 F.3d 1239, 1248 (11th Cir. 2018) (citation omitted). It is enough that more of the drug leads to more of the disease.

The experts here pointed to exactly this kind of evidence with respect to ranitidine and NDMA. They "base[d] their opinion" that "use of ranitidine can cause cancer" in part on "the evidence of a positive dose-response effect." MDL.Dkt.6171-9 at 18 (McTiernan); *see also supra* note 17. For bladder cancer, the experts pointed to the Cardwell study, which showed (in the authors' own words) "a 22% increased risk of bladder cancer in ranitidine users, which *increased* to 43% in participants using *more than 3 years* of ranitidine." MDL.Dkt.6185-31 at 7 (emphasis added). For liver cancer, the experts pointed to the Wang study, which showed (in the authors' own words) "when *considering the dose-response* of ranitidine usage, there were significant trends of increased liver cancer risk with an increasing dose of ranitidine." MDL.Dkt.6061-6 at 14 (emphasis added).[21] For the remaining three cancers, the experts relied on studies showing that more NDMA led to more cancer. *See supra* note 17. This is exactly what is required to show dose-response: that a "change in amount, intensity, or duration of exposure" to the NDMA

[21] The district court stated that "[s]ome ranitidine studies attempted to observe evidence of a dose-response relationship between high levels of ranitidine consumption and cancer, but no study concluded such a relationship existed." MDL.Dkt.6120 at 261. This is simply wrong: Wang and Cardwell both concluded there *was* dose-response. MDL.Dkt.6061-6 at 14; MDL.Dkt.6185-31 at 7.

in ranitidine "is associated with ... an increase ... in risk" of cancer. *McClain*, 401 F.3d at 1241-42.

Concluding otherwise, the district court offered a single paragraph of analysis as to Drs. McTiernan and Moorman. MDL.Dkt.6120 at 313. Cardwell and Wang were not enough to demonstrate dose-response, the district court held, because the experts had "appl[ied] internally inconsistent principles to analyze the data in Cardwell and Wang," "selectively extract[ed] data points," and "deviate[d] from the study authors' conclusions." *Id.* But as explained above, the Cardwell and Wang study authors *themselves* suggested their studies showed evidence of dose-response. The district court did not explain why these results were insufficient.

The district court also erred by holding that the experts failed to rely on evidence on an issue "related to, yet *distinct from* dose-response," namely "threshold dose," MDL.Dkt.6120 at 301 (emphasis added), the dose "range at which ranitidine can cause cancer," *id.* at 33. As discussed earlier with regard to category 1 cases, dose is properly considered a *specific* cause issue. Requiring a threshold dose has no basis in Bradford Hill analysis.

Even if it were required, the experts here did rely on evidence showing this range. For bladder cancer, the Cardwell study showed that a range between 0 and 3 years was enough to cause cancer, because patients taking Zantac for three years or more showed a statistically significant 43% higher risk. For liver and gastric cancer,

the Wang study showed that a range between 0 and 1 year was enough to cause cancer, because patients taking Zantac for one year or more showed a statistically significant 42% (liver) and 33% (gastric) higher risk, respectively. These results are sufficient to establish the "levels of exposure that are hazardous to human beings generally." *McClain*, 401 F.3d at 1241 (citations omitted). And these doses are realistic, since "60% of Plaintiffs allege they used ranitidine for more than ten years." MDL.Dkt.6174 at 62.

The district court recognized that the experts "cite levels at which NDMA can cause cancer based on Cardwell and Wang," but rejected this evidence because the experts "do not opine that these levels are *minimum* threshold dose levels." MDL.Dkt.6120 at 314 (emphasis added). This makes no sense. If a dose is *sufficient* to increase the risk of cancer—which the studies establish—*Daubert* does not require exclusion just because an expert cannot identify the *theoretical* minimum necessary dose.

For example, although ten cigarette pack-years are known to be associated with higher risks of lung cancer, nobody can say what the theoretical minimum is—one pack-year? One pack? One cigarette? It would make no sense to forbid an expert to testify that smoking causes cancer just because she cannot say whether one pack is enough (though, of course, that could be grounds for exclusion under *specific* causation for a plaintiff that consumed just one pack). The point is the same for

ranitidine. But that is what the district court did, holding that failure to identify the theoretical minimum dose warranted exclusion. *See id.* at 313 (criticizing Le and Melnick for not identifying a dose "at which NDMA is *not* carcinogenic in humans" (emphasis added)); MDL.Dkt.6120 at 313 (criticizing Panigrahy, Michaels, McTiernan, and Moorman for not identifying a "threshold amount of NDMA that *does not* cause cancer" (emphasis added)). The district court identified not a *single* scientific authority saying that it is unreliable for scientists to focus on sufficient rather than bare-minimum exposure levels. In fact, what Plaintiffs' experts did is routine in the scientific literature, especially for genotoxins (which scientists believe *have* no threshold dose). *See supra* note 6.

D. The District Court Erroneously Took Sides in an Ongoing Scientific Debate.

In addition to misclassifying this case under *McClain* and (wrongly) concluding that the experts failed to rely on a primary methodology, the district court also flouted this Court's requirement that the *Daubert* court must "meticulously focus on the expert's principles and methodology, and not on the conclusions that they generate." *McDowell*, 392 F.3d at 1298. Here, the court *began* by discussing conclusions for eleven pages, MDL.Dkt.6120 at 170-80, finding that the experts' causation *conclusions* were suspect because the underlying epidemiology studies had not used the magic word "causation" in the studies' *own conclusions*—

something such studies rarely do, and which ample case law makes clear is *not* a basis for exclusion.

Beginning from the (faulty) premise that the conclusions were suspect, the district court broke down each opinion "atomistically," over more than one hundred pages, falsely assuming that their "ultimate opinion" on causation "was *independently* supported by each" plank of evidence, *Milward*, 639 F.3d at 23, and in many instances wrongly finding "gaps" in those specific planks "of [its own] making," *id. See also In re Bair Hugger Forced Air Warming Devices Prod. Liab. Litig.*, 9 F.4th 768, 779 (8th Cir. 2021) (criticizing the district court for wrongly "contribut[ing] to the analytical gap it found"). In doing so, the district court repeatedly weighed "the persuasiveness of the proffered evidence," *Quiet-Tech*, 326 F.3d at 1341, improperly determined "which of several competing scientific theories has the best provenance," *id.*, and ultimately "took [a] side[] on questions that are currently the focus of extensive scientific research and debate," *Milward*, 639 F.3d at 22.[22] In short, the district court arrogated to itself the power to "view[] the

[22] Taking sides was inevitable in light of the studies. For example, one study found "evidence of an increased risk of bladder cancer in ranitidine users." MDL.Dkt.6185-31 at 2 (Cardwell). Another found "little evidence of any substantially increased risk of bladder [cancer]." MDL.Dkt.6187-20 at 7 (Norgaard). There is no way to square those results without passing on the "persuasiveness of competing scientific studies," *Quiet-Tech*, 326 F.3d at 1341—something the district court is forbidden from doing, *id.*, but what it eagerly did here.

universe of ranitidine studies in the totality," and "agree[] with the Defendants." MDL.Dkt.6120 at 178. That overstepped its proper role under *Daubert*.

1. The district court erroneously required a study to say the word "causation" before allowing an expert to rely on it.

Shading the district court's *entire* analysis of the epidemiology was its oft-repeated assertions that "the Plaintiffs' experts have no independent, epidemiological scientific support for their conclusions." MDL.Dkt.6120 at 250. This is a breathtaking statement. The Cardwell study expressly stated: "we observed a 22% increased risk of bladder cancer in ranitidine users, which increased to 43% in participants using more than 3 years of ranitidine (1,095 DDDs)." MDL.Dkt.6185-31 at 7. And the Wang study expressly stated: "The conclusive results of our study after gathering data emphasize that consuming high levels of NDMA due to ranitidine use is linked to liver cancer development." MDL.Dkt.6061-6 at 14 (Wang). The McDowell study "found a statistically significant, positive association between ranitidine use and pancreatic cancer." MDL.Dkt.6120 at 175. And there are numerous other positive findings. *E.g.*, *supra* note 18.

Despite over-the-top rhetoric, what the district court *really* meant is that the studies were missing the magic word "causation." *See, e.g.*, *id.* at 173 (stating that "researchers did not conclude" *definitively* in their text that "ranitidine caused cancer"). Over-and-over-again, the district court harped on this trivial theme. *See id.* at 6 ("None of the ranitidine-focused epidemiological studies concluded that

ranitidine causes cancer."); *id.* at 177 ("[T]here is no published conclusion or finding, outside of this litigation, that concludes that ranitidine causes cancer of any kind."); *id.* at 169 (crediting Defendants' argument that "no scientist outside of this litigation has concluded that ranitidine can cause cancer"); *id.* at 180 ("[T]here is no widespread acceptance that ranitidine causes cancer."); *id.* at 228 ("Dr. McTiernan does not rely upon the conclusion of any study to support her opinion that ranitidine causes cancer, because no published study has ever reached that conclusion."); *id.* at 250 ("[N]o publication or scientist has concluded ... ranitidine can cause cancer."); *id.* at 259 ("[T]here is no ranitidine epidemiology that concludes that ranitidine causes cancer."); *id.* at 281 ("[N]o independent scientist or publication has concluded that ranitidine causes cancer."); *id.* at 299 ("[T]he Plaintiffs' experts make analytical leaps that no scientist outside of this litigation has made."). Indeed, the district court suggested that the lack of "causation" language in the epidemiology studies was *determinative*: this purported "lack of independent scientific support is a valid ground for the Court to grant the Defendants' Epidemiology Motion because it is a valid ground for the Court to question the reliability of the Plaintiffs' experts' methodologies." *Id.* at 177.

This was mistaken. There is no requirement that a study say the magic word "causation" before an expert may use that study (in combination with other evidence) to support a causation opinion. Even when a study "disclaims" proving

causation, it is not "*per se* unreliable for an expert to draw an inference of causation." *Bair Hugger*, 9 F.4th at 779. To the contrary, the *Daubert* cases uniformly hold that experts *may* provide general causation testimony *even when* the underlying studies do *not* say that they have demonstrated causation. *See Bair Hugger*, 9 F.4th at 779 ("[I]t was not necessarily unreasonable for the experts to rely on [a study] to draw an inference of causation just because the study itself recognized, consistent with [epidemiology] principles, that the association did not establish causation."); *Knight v. Kirby Inland Marine Inc*., 482 F.3d 347, 354-55 (5th Cir. 2007) (An expert need not "back [their] opinion with published studies that unequivocally support [their] his conclusions."); *Amorgianos v. Nat'l R.R. Passenger Corp.*, 303 F.3d 256, 266 (2d Cir. 2002) (rejecting the notion "that an expert must back his or her opinion with published studies that unequivocally support his or her conclusions"); *Bonner v. ISP Techs.*, *Inc.*, 259 F.3d 924, 929 (8th Cir. 2001) ("There is no requirement 'that a medical expert must always cite published studies on general causation in order to reliably conclude that a particular object caused a particular illness.'" (citation omitted)); *McCullock v. H.B. Fuller Co.*, 61 F.3d 1038, 1043 (2d Cir. 1995) (allowing the expert to testify even though he "could not point to a single piece of medical literature that says [the substance] causes [the disease]"); *United States v. W.R. Grace*, 504 F.3d 745, 765 (2d Cir. 2007) ("The fact that a study is associational" rather than "intended to show causation" "does not bar it from being

used to inform an expert's opinion."); *In re Ephedra Prods. Liab. Litig.*, 393 F. Supp. 2d 181, 188 (S.D.N.Y. 2005) (rejecting any *Daubert* rule that would "automatically exclude causation testimony unless it is based on ... studies" *stating* that a substance causes a certain disease). Any "lack of textual support"—*i.e.*, epidemiologists' reluctance to use the word "causation"—may "go to the weight" of the evidence, but "not the admissibility." *Knight*, 482 F.3d at 354-55 (citation omitted).

There is a very good reason why courts do not require epidemiology studies to say "causation" before allowing an expert to opine about it, namely that "[e]pidemiology *cannot prove* causation." *Reference Manual* at 598 (emphasis added). "Epidemiology enables experts to find *associations*, which by themselves do not entail causation," and "ultimately 'causation is a *judgment* for epidemiologists and others interpreting the epidemiologic data.'" *Bair Hugger*, 9 F.4th at 779 (citations omitted); *Milward*, 639 F.3d at 18 (determining causation requires "the use of scientific judgment" to determine whether "an association truly reflects a causal relationship or is spurious"). There is "no algorithm" for determining causation. *Milward*, 639 F.3d at 18. And because "no scientific methodology exists for this process," "reasonable scientists may come to *different* judgements about whether such an inference is appropriate." *Id.* (emphasis added) (citation omitted).

Because causal inferences are nuanced judgments based on *all* the evidence, it is never a surprise—or indicative of unreliable methodology—when an expert

giving a causation opinion relies on a study that itself does not "prove causation." *Id.* at 24-25.[23] None of the studies in this litigation purported to consider all the evidence and draw a causal inference—the conclusions, therefore, were about what could be proven *based on that study alone*. The experts, by contrast, looked at all the evidence, and so they—unlike the study authors—could come to a conclusion on causation. *Milward*, 639 F.3d at 18.[24] The district court should not have excluded the experts on this basis.

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[23] The Wang study authors state in no uncertain terms that "the clear data from our real-world observational study strongly support the pathogenic role of NDMA contamination, given that long-term ranitidine use is associated with a higher likelihood of cancer development." MDL.Dkt.6061-6 at 13 (Wang). This statement about NDMA's "pathogenic role" in ranitidine comes close—and as close as a single study is likely to get—to saying that ranitidine *causes* cancer. The district court recognized this, admitting that Wang "could be interpreted as [itself] concluding ranitidine causes liver cancer." MDL.Dkt.6120 at 289. Nevertheless, the district court persisted in creating a fictitious parallel universe in which the experts had "*no* independent, epidemiological scientific support for their conclusions." *Id.* at 250.

[24] The district court places great emphasis on the Florian study, performed in conjunction with the FDA, and its statement that "no consistent signals emerged across [epidemiological] studies." MDL.Dkt.6120 at 177 (quoting Florian 2021 at 241). But the timeline makes this statement meaningless: that study did not consider the Cardwell and Wang studies. And the Florian study was *not* an exhaustive review of even the literature in existence at the time. It was instead "a human clinical trial"—conducted on patients' urine—"to determine whether ranitidine degrades into NDMA in the human body." *Id.* at 5. The same issue plagues the EMA assessment report relied on so heavily by the district court: it was published in 2020, one year before Cardwell and two years before the Wang, making irrelevant its purported "comprehensive review of epidemiological and post marketing data." *Id.* at 177 (quoting EMA, Assessment report at 18).

2. The district court erroneously held that the experts could not rely on results unless they were statistically significant.

Continuing in its pattern of deciding for itself which studies were valid and which were not, the district court wrongly held that the experts were not entitled to rely on study results lacking statistically significance. *See also* MDL.Dkt.6120 at 165 ("For a [risk] ratio to generally be helpful in a causation inquiry it must be statistically significant."); *id.* ("[A]s a general matter, [a statistically insignificant] study finding is not helpful to a causation inquiry."). This again was error. As the Supreme Court has noted, "medical professionals and researchers do not limit the data they consider to ... statistically significant evidence" "to establish an inference of causation." *Matrixx Initiatives, Inc. v. Siracusano*, 563 U.S. 27, 40-41 (2011). Neither does the FDA. *Id.* And "courts frequently permit expert testimony on causation based on evidence other than statistical significance." *Id.* at 40-41. For this reason, the "premise that statistical significance is the only reliable indication of causation ... is flawed." *Id.* at 40; *Reference Manual* at 579 (noting that epidemiologists do not "reject[] all studies that are not statistically significant"). "Simply put, studies in which there are true causal effects may yield results that are not statistically significant." Kenneth J. Rothman, et al., *Modern Epidemiology* 76 (4th ed. 2021). As this Court has explained, "Plaintiffs' burden of proving [the injuries] were caused by the Product did not necessarily require them to produce scientific studies showing a statistically significant association." *Wells v. Ortho*

Pharm. Corp., 788 F.2d 741, 745 (11th Cir. 1986). "Products liability law does not preclude recovery until a 'statistically significant' number of people have been injured." *Id.* (citation omitted).

The ATSDR, citing Professor Rothman's authoritative position and applying the Bradford Hill factors, has similarly discouraged emphasis on statistical significance in performing causal assessments:

> In our assessment, we *did not use confidence intervals to determine whether a finding was 'statistically significant'* nor did we use significance testing to assess the evidence for causality (Rothman et al. 2008). There are several limitations to the use of statistical significance testing (Rothman et al. 2008, Goodman 2008, Stang et al. 2010). Moreover, a finding that does not achieve statistical significance nonetheless can provide important evidence for a causal association, while a finding that achieves statistical significance can often lack scientific and public health significance. Because of the limitations of statistical significance testing, it was not used to assess the epidemiological evidence.

ATSDR, *Assessment of the Evidence for the Drinking Water Contaminants at Camp Lejeune and Specific Cancers and Other Diseases* (2017) (emphases added).

The reason epidemiology textbooks, precedents, government agencies, and the *Reference Manual* consider results that are not statistically significant is a basic one: When a study result is positive but not statistically significant, that *still* means that *more* people exposed to a substance developed a disease than people who were not exposed to the substance. *See Reference Manual* ("If the relative risk is greater

than 1.0 ... there is a positive association between exposure to the agent and the disease, which *could be causal*."). When determining whether a substance causes a disease, an epidemiologist is entitled to consider the fact that more people developed the disease after being exposed to the substance. That is all the experts did here.

Nevertheless, the district court repeatedly criticized the experts for relying on non-statistically significant results. *See* MDL.Dkt.6120 at 7 (criticizing experts for "a lack of statistically significant data"); *id.* at 228 (criticizing Dr. McTiernan for "disregard[ing] the concept of statistical significance"); *id.* at 229 ("[Dr. McTiernan] disregards the concept of statistical significance."); *id.* at 231 ("In summary, Dr. McTiernan relies upon bladder cancer ranitidine epidemiology with statistically insignificant data."); *id.* at 235 (criticizing Dr. McTiernan for "rel[ying] upon the statistically insignificant risk rates in Tran"); *id.* at 243 (criticizing Dr. McTiernan for "'disregard[ing] the concept of statistical significance'"); *id.* at 243 (criticizing Dr. McTiernan for refusing to "choose *not* to rely upon findings *because of* the statistical insignificance of those findings"); *id.* at 264 (criticizing Dr. McTiernan's purported "disregard of statistical significance"); *id.* at 290 (criticizing "Plaintiffs' experts" for premising their analysis "on much statistically insignificant data"); *id.* at 297 ("the three non-epidemiologists ... rely upon statistically insignificant data"). To be clear, though the district court accused the experts of disregarding statistical significance, it is undisputed that the experts reported and discussed confidence

intervals and statistical significance in their reports. The district court simply thought they did not care about it *enough*.

For example, the district court's opinion contained the following chart:

Id. at 201. The chart shows that in three separate studies, users of ranitidine developed bladder cancer at higher rates—5%, 11% and 41% higher—than users of similar antacid medications. That is simply a mathematical fact. Is an epidemiologist entitled to consider that fact when deciding whether ranitidine—which contains a known carcinogen that exits the bladder—might cause bladder cancer? Of course he is—and he should. Yet the district court held that the experts were *unreliable* for even *considering* this kind of evidence because doing so somehow "'disregards the concept of statistical significance.'" *Id.* at 243. That was error. *See Matrixx Initiatives, Inc.*, 563 U.S. at 41 ("Medical professionals and researchers do not limit the data they consider to ... statistically significant evidence." (citation omitted)).

Although some courts have "frowned on causative conclusions *bereft* of statistically significant epidemiological support," MDL.Dkt.6120 at 255 (emphasis added) (quoting *Wells v. SmithKline Beecham Corp.*, 601 F.3d 375, 380 (5th Cir. 2010))—*i.e.*, situations where an expert is relying *only* on non-significant results—

that is not the situation here. For *each of* the five cancers, there was at least one statistically significant result, and often more than one. *See* MDL.Dkt.6185-31 (Cardwell) (Bladder); MDL.Dkt.6187-15 (Liu), MDL.Dkt.6187-5 (Habel), MDL.Dkt.6061-6 (Wang) (Gastric); MDL.Dkt.6185-28 (Adami), MDL.Dkt.6187-5 (Habel) (esophageal); MDL.Dkt.6187-9 (Kantor), MDL.Dkt.6061-6 (Wang) (liver); MDL.Dkt.6187-18 (McDowell), MDL.Dkt.6187-5 (Habel), MDL.Dkt.6061-6 (Wang) (pancreatic). The positive non-significant results buttress those statistically significant findings as part of the experts' holistic review of the evidence. The district court was therefore wrong to view the experts' reliance on all the results, including the non-significant ones, as evidence that the experts' methodologies are unreliable.

3. The district court wrongly held that studies showing positive, non-statistically significant results were evidence of *no* increased risk.

The district court's misunderstanding of statistical significance is compounded when analyzing studies showing *increased* risks that were not statistically significant. The district court interpreted all such results as *affirmative* evidence showing that Zantac *does not* cause cancer. *See* MDL.Dkt.6120 at 177 (describing these studies as providing "a large amount of evidence ... that there is no link between ranitidine consumption and cancer"). And it criticized the experts' conclusions for being inconsistent (or even contradicted by) those studies. *See id.* at 296 (criticizing experts for "disregarding the active comparator analyses in other

studies that were statistically insignificant and were less favorable to their expert opinions"); *id.* at 177 (holding that the purported "evidence that there is no link between ranitidine consumption and cancer" demonstrated "lack of independent scientific support" and provides "a valid ground for the Court to grant the Defendants' Epidemiology Motion").

This was doubly wrong. As an initial matter, absence of evidence is not evidence of absence. Especially for a disease like cancer, a study showing no association cannot provide evidence that there is *no* increased risk unless the study runs for 30 *years*, IARC, *IARC Monographs on the Identification of Carcinogenic Hazards to Humans: Preamble* 22 (amended 2019) ("[L]atency periods substantially shorter than about 30 years cannot provide evidence of lack of carcinogenicity."), and the studies here were nowhere near that long.[25] *See* MDL.Dkt.6179-7 at 11 (Moorman Rebuttal) ("None of the studies had adequate follow-up time to capture the full latency period of cancer development, but several of the studies had such short follow-up times that they were virtually guaranteed not to detect an increased risk of cancer with ranitidine use."); MDL.Dkt.6171-9 at 28, 31, 67-68, 138, 153-56 (Table 4) (McTiernan) (same).

[25] The median follow-up in years was: 2.4 MDL.Dkt.6187-7 (Iwagami); 4.4 MDL.Dkt.6187-13 (Kumar); 6.7 MDL.Dkt.6187-9 (Kantor); 7 MDL.Dkt.6187-29 (Yoon); 12-14 MDL.Dkt.6185-28 (Adami); 11-14 MDL.Dkt.6187-20 (Norgaard).

More importantly, the positive but statistically insignificant results here are evidence that *there is* a risk. For example, the district court viewed the Yoon study as providing "evidence that there is no link between ranitidine consumption and cancer." MDL.Dkt.6120 at 177; *see id.* at 175 (summarizing the Yoon study). But patients exposed to ranitidine in that study developed cancer at a 41% *higher* rate than patients who consumed other antacids. *See* MDL.Dkt.6187-29 at 5. The result was not statistically significant (with an outer range suggesting the increased risk could be as much as 224%), but that does not take away from what happened: patients who took ranitidine developed cancer at markedly higher rates than those who took the comparator antacid. One can hypothesize that chance *might* explain some of the effect, but a true association is an even more likely explanation. And, either way, the fact that patients taking ranitidine developed *more* bladder cancer is obviously not "evidence that there is *no link* between ranitidine consumption and cancer." MDL.Dkt.6120 at 177 (emphasis added). The district court erred by holding to the contrary.

4. The district court wrongly held that the experts 'disregarded' active comparator studies.

Based in part on its misunderstanding of the true meaning of positive but statistically insignificant results, the district court wrongly held that the experts had entirely "disregarded" the active-comparator studies—many of which showed non-significant positive results. *See, e.g.*, *id.* at 183 ("Plaintiffs' experts contend that all

ranitidine epidemiology findings based upon active comparators should be disregarded."); *id.* at 199 (referring to "Plaintiffs' experts' decision to disregard active comparator study designs"); *id.* at 193 n.99 ("Plaintiffs' experts have provided no justification for the idea that all ranitidine active comparator analyses should be disregarded."); *id.* at 183 ("Plaintiffs' experts contend that all ranitidine epidemiology findings based upon active comparators should be disregarded."); *id.* at 290-91 ("Dr. McTiernan did not rely upon active comparator analyses as part of her final analysis."); *id.* at 257 (referring to Dr. McTiernan's purported "decision to disregard all active comparator analyses"); *id.* at 264 (referring to Dr. McTiernan's purported "disregard of active comparators"); *id.* at 257 (stating that Dr. McTiernan has demonstrated a "selective disregard for data within a study that does not tend to support her conclusions (active comparisons)").

In reality, the experts did not "disregard" these active comparator studies. The experts cited, quoted, and analyzed every single study in exhaustive detail—including the Wang study and Cardwell studies, which themselves use active-comparators, and which provide powerful support *in favor* of the experts' opinions.

By "disregard," the district court meant that the experts concluded that the defendants' preferred active-comparator studies, given their limitations, were not enough to counterbalance the weight of the evidence favoring causation. The district court was simply "weigh[ing] [and] assess[ing] the correctness of competing expert

opinions," *Johnson*, 754 F.3d at 562, and evaluating "the persuasiveness of competing scientific studies"—which it is forbidden to do, *Quiet Tech.*, 326 F.3d at 1341. Although "epidemiology" is a recognized type of primary methodology in the Eleventh Circuit, *Chapman*, 766 F.3d at 1301, there is no rule requiring any particular *varietal* of epidemiology—like active-comparator studies—to be given more weight.[26] This is especially true because "all studies have 'flaws' in the sense of limitations that add uncertainty about the proper interpretation of the results." *Reference Manual* at 553. Study designs and limitations vary tremendously, and no bright-line rule could ever capture even approximately the nuanced judgment required to determine which evidence deserves the most weight.

After wrongly deciding that the experts had "disregarded" the active-comparator studies, the district court arrogated to itself the power determine the experts' "real" reasons for doubting that those studies provided the definitive answer on causation. In the district court's telling, this purported "disregard" was based

[26] At times the district court was forced to parse even the active-comparator literature more closely to define "reliable" studies. After all, there are multiple studies showing that patients taking Zantac developed cancer at higher rates than patients taking PPIs, another antacid. *E.g.*, MDL.Dkt.6185-31 (Cardwell) (1.2 versus PPIs); MDL.Dkt.6187-9 (Kantor) (1.3 versus omeprazole, non-statistically-significant); MDL.Dkt.6187-20 (Norgaard) (1.24 versus PPIs). But the district court held that only studies comparing ranitidine to H-2 blockers would suffice. MDL.Dkt.6120 at 188. And when the Wang study appeared, the district court found that was not enough either. *Id.* at 296-97.

exclusively on two (and only two) reasons. MDL.Dkt.6120 at 191 ("To contest the decision by the eight study authors to compare ranitidine to competing medications to help control for confounding, the Plaintiffs' experts offer two critiques."). First, the experts' belief that the two patient populations were "*not* similar." *Id.* at 192. And second, the experts' belief that "every [active comparator] causes cancer." *Id.* at 194.

This is not a faithful account of the experts' opinions. Although the experts mentioned that the other antacids might themselves increase the risk of cancer for various reasons,[27] and although the experts mentioned that the patient populations might not be similar,[28] those were *not* the only criticisms they leveled, nor even the most significant. To the contrary, the experts explained that the active-comparator studies understated the true cancer risk because they were too short to detect many

[27] A recent study shows that the experts were correct in this criticism—and vividly illustrates the dangers of a federal judge playing the role of scientist. In 2023, *after* the district court's ruling, the Safdari study showed that famotidine—one of the H2 blockers that the district court deemed to be the only kind of valid comparator—itself might degrade into NDMA. *See* Amin Safdari et al., *Investigating the Possibility of N-Nitrosodimethylamine (NDMA) in Famotidine Containing Products*, 88 J. Drug Delivery Sci. & Tech. (2023). That would make famotidine an inappropriate comparator to use for evaluating the risk of cancer from ranitidine.

[28] The experts had sound reasons for saying this. In the one study that gathered extensive data on the comorbidities of the two patient populations, the *comparator* group was uniformly sicker—more likely to smoke, drink, have diabetes, have high blood pressure, etc. *See* MDL.Dkt.6179-7 (Moorman Rebuttal) at 8 (citing the MDL.Dkt.6187-12 (Kim Y. study)).

cancers, did not include enough patients with substantial Zantac use—in many cases, just one prescription—failed to account for OTC use, and *many* other reasons. *See, e.g.*, MDL.Dkt.6179-7 at 7 (Moorman Rebuttal) (criticizing the "active-comparator studies" because "key assumptions for the proper use of active comparator studies were not met," and the "studies had numerous other limitations and sources of bias, including incomplete assessment of ranitidine use, misclassification of exposure, inadequate follow-up time, inappropriate study populations, lack of information on important confounders, and potential conflicts of interest."); MDL.Dkt.6179-6 at 71-88 (Moorman); MDL.Dkt.6171-9 at 98-100 (McTiernan).

The district court seemed aware that the experts had these "various [other] reasons" "pertain[ing] to criticisms of study design and the like. MDL.Dkt.6120 at 244. But it decided "not [to] discuss those criticisms because they are not relevant to the Court's ultimate conclusions." *Id.* This is not a proper *Daubert* analysis. The district court is not entitled to find that an expert "disregarded" a study—when the expert engages with it in detail—then determine the "real" reasons for this purported disregard, decide that those "real" reasons are unreliable, and then hold without explanation that the *other* reasons given are "not relevant to the Court." *Id.* Any "outcome-driven reasoning," *id.* at 198, was on the part of the district court, not the experts.

5. The district court wrongly held that relying on NDMA studies was *per se* unreliable.

With respect to studies on NDMA, the district court's rule was even more draconian. The district court held that *any* "expert opinions based on those studies [occupational and dietary studies of NDMA] are unreliable." *Id.* at 313; *id.* at 307 ("The Court previously excluded expert opinions premised upon [occupational and dietary studies concerning NDMA]."); *id.* at 227 ("[T]he Court agrees with the Defendants that any expert's reliance upon the dietary and occupation studies discussed above to form a general causation opinion on ranitidine amounts to an unreliable methodology."); *id.* at 216 ("an expert opinion that relies upon the dietary or occupational studies discussed above to conclude that ranitidine can cause cancer utilizes an unreliable methodology"). To be clear, *none* of the experts relied on these NDMA studies *alone*. But according to the district court, *any* reliance on the NDMA studies transforms the expert's opinion into an unreliable one.

There is nothing in *Daubert* that requires an expert to ignore a certain kind of study. The experts here employed a "weight of the evidence" approach, which is presumptively allowed under *Daubert*. *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787, 795 (3d Cir. 2017). When evaluating the evidence about ranitidine and cancer—a drug that undisputedly contains NDMA—that weight of the evidence naturally included evidence about NDMA and cancer. Just as an expert evaluating the addictiveness of cigarettes would consider literature on the

addictiveness of nicotine, the experts here were entitled to consider literature on the carcinogenicity of NDMA when evaluating the carcinogenicity of ranitidine.[29] But in the district court's view, the NDMA studies were a third rail that automatically vaporized the expert's opinion. This was error.[30]

E. The District Court's Reasons for Excluding Drs. McTiernan and Moorman Are Misguided and Designed to Impede This Court's Review.

Attempting to insulate its findings from appellate review, the district court provided *nine* purportedly *independent* reasons to exclude Dr. Moorman and *ten* reasons to exclude Dr. McTiernan, including a catch-all "totality of the evidence"

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[29] Bizarrely, the district court elsewhere acknowledges that "various [independent] scientific authors considered all available evidence on NDMA, including even animal studies," MDL.Dkt.6120 at 255 (footnote omitted), and seemed to concede that "the FDA[] routinely consider[ed] dietary epidemiology," including the dietary epidemiology about NDMA, *id.* 255 n.130. This is impossible to square with the Court's holding that "any expert's reliance upon the dietary and occupation studies [about NDMA] to form a general causation opinion on ranitidine amounts to an unreliable methodology." *Id.* at 227.

[30] After the district court's order, in August 2023, ATSDR issued a public-facing "Tox FAQs" document regarding NDMA. That document fully embraced the NDMA studies that the district court held were *per se* unreliable. ATSDR posed the question "Can NDMA cause cancer?" and then answered as follows: "Some studies show that workers exposed to NDMA may have a greater chance of developing liver, stomach, bladder, and prostate cancer. Ingesting high levels of NDMA may lead to stomach and colorectal cancer. Animals that ate NDMA developed liver, lung, kidney, and testicular cancers." *See* Agency for Toxic Substances and Disease Registry, U.S. Dept. of Health & Human Servs., *N-Nitrosodimethylamine (NDMA) – ToxFAQs*, at 2 (Apr. 2023).

reason. This brief explained above why six of the reasons are mistaken.[31] The other reasons are not grounds for exclusion (nor are they independent).

First, the district court held that a factor "weigh[ing] strongly in favor of exclusion," MDL.Dkt.6120 at 253, was that Dr. McTiernan "fail[ed] to adequately explain to the Court how her opinion is formulated," *id.* at 251. This is just not true. Dr. McTiernan's report explains background concepts, MDL.Dkt.6171-9 at 19-45; discusses NDMA exposure sources and measurement, *id.* at 46-65; canvasses the types of bias and confounding in epidemiologic studies, *id* at 66-98; describes her methodology, *id.* at 98-100; conducts a comprehensive literature review regarding both ranitidine and NDMA, *id.* at 101-84; and performs a Bradford Hill analysis for each cancer (bladder, *id.* at 185-207; esophagus, *id.* at 208-26; liver, *id.* at 227-39; pancreas, *id.* at 239-58; stomach, *id.* at 259-82), then summarizes her conclusions

[31] *Compare* MDL.Dkt.6120 at 250, 281 (excluding the Moorman/McTiernan opinions because "no independent ... scientist outside of this litigation has concluded that ranitidine can cause cancer") *with supra,* at 51-56; *compare* MDL.Dkt.6120 at 256 (excluding McTiernan because she placed "'undue'" reliance on statistically insignificant results) *with supra*, at 56-60.; *compare* MDL.Dkt.6120 at 257, 282 (excluding McTiernan/Moorman because they "disregard[ed]" "all active comparator analyses") *with supra*, at 63-67; MDL.Dkt.6120 at 259, 282 (excluding McTiernan/Moorman because their opinions were "undermined" by studies "which found no statistically significant evidence of an association between ranitidine and cancer"); *with supra*, at 61-63; *compare* MDL.Dkt.6120 at 260, 282 (excluding McTiernan/Moorman because they relied on NDMA studies) *with supra*, at 67-69; *compare* MDL.Dkt.6120 at 262, 283 (excluding McTiernan/Moorman because they lacked "reliable evidence of a dose-response relationship") *with supra*, at 46-49.

and discusses dosage, and includes dozens of pages of summary graphs and charts (282-386). Meanwhile her *three* days of depositions spanned more than 20 hours, during which she provided (repeated) explanations of what, exactly, she did. To the extent the district court did not itself *understand* the (admittedly) scientifically dense report, or the concepts being discussed in the deposition, that is not a basis for exclusion.

Although the district court complains that "the Court does not know what studies (for any cancer) most strongly influence Dr. McTiernan's opinions," MDL.Dkt.6120 at 253," determining causation is a matter of "judgment," *Bair Hugger*, 9 F.4th at 779, and there is "no algorithm" for determining causation via a weight-of-the-evidence approach. *Milward*, 639 F.3d at 18. Dr. McTiernan's approach matches how peer reviewed scientists perform a Bradford Hill analysis outside of the courtroom. It cannot be methodologically unreliable under Rule 702 to mirror the approach independent scientists routinely take to causal questions.

Second, the district court held that Dr. Moorman "selected ... inputs" for her analysis "based upon a results-oriented, conclusion-driven methodology." MDL.Dkt.6120 at 281. But the "inputs" for her analysis were the same "inputs" relied upon by every expert in this litigation, plaintiff or defendant. Dr. Moorman reviewed *all* the evidence (including the studies Defendants emphasized). Neither Defendants nor the court suggested that Dr. Moorman failed to analyze a relevant

study. The *real* basis for the Court's holding is that Dr. Moorman placed greater *emphasis* on certain studies that the district court *itself* deemed less reliable. *See id.* at 280 (taking issue with Dr. Moorman placing greater weight on some NDMA studies than on some ranitidine epidemiology); *id.* at 279 (taking issue with the "'strong'" and "'moderate'" weight that Dr. Moorman placed on certain studies). But *Daubert* law is clear that a district court may "not determine which of several competing scientific theories has the best provenance," *Milward*, 639 F.3d at 15, or evaluate "the persuasiveness of competing scientific studies." *Quiet-Tech*, 326 F.3d at 1341.

Third, the district court held that Drs. McTiernan and Moorman employed a "ranitidine-specific methodology" that "has not been employed by any published scientist or governmental body." MDL.Dkt.6120 at 254. How could this constitute an independent ground for exclusion? The "ranitidine-specific methodology" employed by Dr. McTiernan and Dr. Moorman was a Bradford Hill analysis and weight-of-the-evidence approach—neither is novel, both are presumptively reliable under *Daubert*. *Milward*, 639 F.3d at 18 ("No serious argument can be made that the weight of the evidence approach is inherently unreliable."). The district court's analysis in support of this purportedly independent ground turns out to be the same gripes with the studies relied upon by the experts—that they relied on NDMA studies and did not give as much weight to the active-comparator studies as the district court

would have. *See* MDL.Dkt.6120 at 254 (criticizing the experts' treatment of "active-comparator analyses"); *id.* at 255 (criticizing the experts' treatment of "[NDMA] dietary and occupational studies"). These criticisms are addressed above. *See supra*, at 67-68. In any event, they have nothing to do with the experts' actual *methods* and everything to do with the district court's repeated efforts to "[take] sides on questions that are currently the focus of extensive scientific research and debate." *Milward*, 639 F.3d at 22.

Fourth, the district court held that Drs. McTiernan and Moorman "take inconsistent positions in their criticisms of ranitidine epidemiology." MDL.Dkt.6120 at 262 (McTiernan), 283 (Moorman). Specifically, the court faults them for criticizing some studies for having too-short a follow-up time while relying on studies with similar follow-up times. MDL.Dkt.6120 at 263. This misguided analysis illustrates exactly why, given that "scientific knowledge is far afield from the normal expertise of judges," "they should proceed with caution lest they exceed their grasp." *Allison*, 184 F.3d at 1310. Given the decades-long latency of cancer, when a study with *short* follow-up time detects an increased risk of cancer, that is particularly *compelling* evidence that a substance causes cancer. When a study with short follow-up time *does not* detect an increased risk, that in no way disproves the notion that a substance causes cancer—as numerous authorities recognized. *See* IARC Preamble at 22 ("[L]atency periods substantially shorter than about 30 years

cannot provide evidence of lack of carcinogenicity."). There is therefore nothing "inconsistent" with recognizing that a short study showing a risk is reliable (indeed, arresting) evidence of a risk—and that a short study showing no risk is unsurprising, and not reliable evidence of no risk.

Think of it this way: If a test is prone to return false *negative* results (like studies with short follow-up), that provides good reason to discount negative results (they could be false negatives), but no reason whatsoever to discount *positive* results. To demand a symmetric response to a test prone to false negatives is to demand irrationality. By holding this instead demonstrated a fatal "inconsistency," the district court erroneously transformed good scientific reasoning into an independent ground for excluding the experts. At a minimum, reasonable scientists can disagree on this point, and the district court was forbidden to pick a winning side of a legitimate scientific debate.

Finally, the district court held that "even if the Court is wrong as to some subset of the Court's prior nine conclusions"—which it was—"[w]eighing all factors and evidence in the totality, the Court concludes that, pursuant to *Daubert*, [Dr. McTiernan and Dr. Moorman] methodology is unreliable." MDL.Dkt.6120 at 264-65 (McTiernan), 283 (Moorman). This vague and ungrounded "totality of the evidence" exclusion is simply not valid under *Daubert*—which is why the district court could not muster a single citation for it. Indeed, the fact that the district court

included this as a purportedly *independent* reason for excluding the experts reveals the opinion for what it is: a results-driven attempt to reverse-engineer grounds for excluding the experts. There is only one reason why a district court begins a sentence by saying "even if the Court is wrong"—which this one does, twice, *id.* at 265, 283—before providing a mushy catch-all reason: To stymie appellate review of its errors.[32]

F. The District Court's Reasons for Excluding Dr. Salmon Are Erroneous.

The district court held that Dr. Salmon's opinions on dose-response were unreliable for "seven reasons," *id.* at 307—bringing the total reasons across the experts to twenty-four, including two backup "totality of the evidence" reasons—but none of them are sound, and all of them merely demonstrate the district court's improper quest to insulate its opinion from meaningful review.

First, the district court noted that Dr. Salmon had relied on occupational and dietary studies linking NDMA to cancer and held—"[f]or this reason alone"—that his opinions were unreliable. *Id.* As explained above, this makes no sense. There is no *Daubert* rule forbidding an expert from relying on a certain type of study—especially a study concerning the exact molecule at issue—and certainly no rule

[32] The district court excluded the epidemiology testimony of Drs. Michaels, Le, and Salmon for these same reasons (and without expert-specific analysis), holding that "there is no meaningful difference between" their epidemiology opinions and those of Drs. McTiernan and Moorman. MDL.Dkt.6120 at 297. The district court erred in excluding those opinions for the same reasons given above.

requiring wholesale exclusion of an expert's *entire* opinion just because he considered a certain type of evidence. *See supra*, at 68-69.

Second, the district court noted that Dr. Salmon had relied upon "consumer experience testing" conducted by Emery Pharma—an independent laboratory that submitted the citizen petition that ultimately led to the ranitidine recall—and excluded his opinion "[f]or this reason alone," because "[t]he Court previously excluded expert opinions premised upon Emery Pharma's testing." MDL.Dkt.6120 at 307. But the consumer experience testing was not the only testing that Dr. Salmon relied upon. He also relied on testing showing the amount of "NDMA reported by the FDA and the Defendants' baseline testing." *Id.* at 304. Although the district court excluded the results of the consumer experience testing, the district court did not doubt the validity of the testing performed by the FDA and the Defendants themselves. *See id.* at 37 (noting no challenge to "the FDA's tests" or "their own tests"). Hence the district court's decision on the consumer-experience testing did not provide a ground to exclude the entirety of Dr. Salmon's testing "[f]or this reason alone." *Id.* at 307.

Third, the district court noted that Dr. Salmon relied upon data from studies done on animals—and held that this, too, was an independent ground for exclusion. *Id.* at 308. But just like studies done on NDMA, studies done on animals are not forbidden fruits when evaluating causation—experts are entitled (as Dr. Salmon did)

to review *all* of the evidence. That is exactly what experts *should* do. The district court erred by concluding that Dr. Salmon should be excluded just because he relied on animal studies as *part of* his opinion.

Fourth, the district court held that Dr. Salmon did not "calculate[] his lifetime cumulative exposure values" according to "a generally accepted methodology." *Id.* Although the district court provided no analysis in support, the fact is that Dr. Salmon's methodology was hardly a novel one. He simply took the amount of NDMA per pill—as demonstrated by FDA and Defendant testing—and then determined how much NDMA would be ingested if a patient took a certain number of those pills for a certain number of years. MDL.Dkt.6185-5 at 225-28 (Salmon). That math is hardly outside of the mainstream and provides no basis for exclusion.

Fifth, the district court criticized Dr. Salmon for emphasizing "data from studies showing a positive dose-response relationship," according to "the WHO's methodology." MDL.Dkt.6120 at 308. That was unacceptable, the district court held, because "regulatory agencies" like the WHO "utilize a more conservative calculus than those applicable in tort law." *Id.* This reasoning is non-responsive. When looking for dose response, the question is simply whether taking more of the drug leads to more of the relevant outcome. Employing WHO methods, Dr. Salmon reviewed the data and answered "yes" to that question. MDL.Dkt.6185-5 at 228 (Salmon). Whether the regulatory agencies employ a more conservative approach

than tort law *when determining to withdraw a drug from the market* says nothing about whether a regulatory agency's methodology when evaluating dose-response and performing a risk assessment are *reliable*.

Sixth, without ever citing or discussing Dr. Salmon's report, the district court held that it was "not clear" that Dr. Salmon followed the WHO methodology because WHO discussed statistical significance. MDL.Dkt.6120 at 308-09. To begin with, the district court should not have excluded an expert just because it inferred that the expert might not have followed a given method based on a stray comment in a brief—analysis of the actual method is required. Had the district court examined the report, it would have seen that Dr. Salmon did indeed follow the WHO methodology, including by using statistically significant results in his calculation. MDL.Dkt.6185-5 at 226 (Salmon) (the numbers under "CI" are above 1.0, which indicates statistical significance).

Finally, the district court held that Dr. Salmon "applies internally inconsistent principles to analyze the data in Cardwell and Wang." MDL.Dkt.6120 at 309. Again, there is no analysis from the district court, but again, the district court is mistaken. Dr. Salmon's dose-response opinion is that more ranitidine leads to more

cancer, and that is exactly what Cardwell and Wang showed. MDL.Dkt.6185-31 at 6-7 (Cardwell); MDL.Dkt.6061-6 at 8 (Wang).[33]

III. The District Court Violated Appellants' Due Process Rights In Applying Its *Daubert* Ruling To All Cases.

This Court should vacate the judgment against the many Appellants who filed claims *after* the district court's *Daubert* order and never had any opportunity to contest general causation with their own experts and record.

After the *Daubert* order, the district court took remarkable steps to enter judgment in every case and to insulate its *prior* rulings from review. As discussed above (and in the Generic-Only brief), Plaintiffs' Leadership disclosed certain experts for general causation to be used in personal injury bellwether trials. The Brand Defendants moved to exclude these experts under *Daubert* and for summary judgment on the element of general causation, which the court granted. MDL.Dkt.6120.

The district court then ordered *every* plaintiff to show cause why summary judgment should not be entered, noting that because the *Daubert* order is "law of the case," any plaintiff claiming not to be bound by the *Daubert* order would have to

[33] The district court did not provide a list of independent reasons for excluding Drs. Panigrahy, Le, Michaels, and Melnick. As best Appellants can tell, they were excluded for failing to employ a "primary methodology." MDL.Dkt.6120 at 321 ("Because the Plaintiffs lack primary evidence, under Eleventh Circuit case law, all of the Plaintiffs' general causation experts are stricken"). Appellants explain above why that holding was error. *See supra*, at 41-44.

"address how the law of the case could be different for any individual late-filing Plaintiff." MDL.Dkt.6444 at 16. In the district court's view, "[i]f the Eleventh Circuit affirms this Court's *Daubert* ruling, that affirmance should apply to every personal injury claim in this MDL." MDL.Dkt.6303 at 20. As explained in the Generic-Only Opening Brief, the district court further demonstrated that the cases were merged by these orders.

Consistent with that view, the district court applied the *Daubert* order not only to the bellwether plaintiffs, but also to *every* plaintiff in the MDL, with no opportunity to present another expert. Incredibly, the court applied the order to plaintiffs who filed cases *after* the experts were disclosed (and thus could not possibly have agreed to use those experts), and even plaintiffs who filed cases *after the Daubert order was issued*. As the district court saw it, "*The Plaintiffs*" as an undifferentiated whole, "made their best argument as to why their evidence was sufficient to show that ranitidine can cause cancer, but *the Plaintiffs* were unsuccessful." MDL.Dkt.6303 at 19-20 (emphasis added). In the Court's words, its "own understanding, based upon what it learned at the *Daubert* stage of these proceedings, [is] that the theoretical potential of ranitidine to cause cancer would be the same for every Plaintiff." MDL.Dkt.6622 at 5. Thus, "the Court's prior summary judgment ruling applies to every Designated Cancer case in this MDL." MDL.Dkt.6622 at 6. Many Plaintiffs never "consented to using the slate of experts"

excluded by the court, and "strongly" wished to retain their own. MDL.Dkt.6540 at 2. The court rejected this request out of hand. MDL.Dkt.6622 at 6.

The district court also granted summary judgment on claims against the non-Brand Defendants *sua sponte* under Rule 56(f). MDL.Dkt.6622 at 21. To further insulate its previous orders, the district court *vacated* a years-old Rule 54(b) judgment in favor of the Generic Defendants—even though Generic Defendants never asked it to—solely "to include an additional ground for the dismissal: the Court's entry of Rule 56(f) summary judgment on general causation grounds because the Court's 56(f) ruling applied to every Designated Cancer claim." MDL.Dkt.6974 at 5. As Appellants told this Court in motions' practice, the district court lacked authority to add a *new* ground under the federal rules.

Appellants are aware of no other case—whether in an MDL or outside it—where a district court barred a party from proffering the expert witness of his choice and then granted summary judgment because a *different* plaintiff's expert was excluded. Doing so violates fundamental due process principles.

Every plaintiff has a "fundamental" due process right to "be heard 'at a meaningful time and in a meaningful manner.'" *Mathews v. Eldridge*, 424 U.S. 319, 333 (1976) (quoting *Armstrong v. Manzo*, 380 U.S. 545, 552 (1965)). Litigants who "never had a chance to present their evidence and arguments on the claim" cannot be precluded from doing so even where "one or more existing adjudications of the

identical issue ... stand squarely against their position." *Blonder-Tongue Lab'ys, Inc. v. Univ. of Ill. Found.*, 402 U.S. 313, 329 (1971). A district court's "own understanding" about "the theoretical potential of ranitidine to cause cancer" simply makes no difference in that calculus. MDL.Dkt.6622 at 5.

It is not clear what doctrine the district court relied upon in barring any plaintiff from proffering his own expert, but no doctrine justifies it. To start, there was no consent or adoption of the expert witnesses here. In many MDLs, the court will give plaintiffs the option of adopting Plaintiffs' Leadership's experts, or presenting their own. *E.g.*, *In re Denture Cream Prods. Liab. Litig.*, 204 F. Supp. 3d 1348, 1350 (S.D. Fla. 2016) (requiring plaintiffs to choose whether to retain their own experts). In that circumstance, *consent* grounds the application of a *Daubert* order to other cases. Here, there was never any such opportunity—to the contrary, the district court placed a threshold burden on new plaintiffs "to seek to change the Court's mind" on "the theoretical potential of ranitidine to cause cancer" before they could even submit a new expert. MDL.Dkt.6622 at 5.

The district court suggested that "law of the case" prevented relitigation of general causation, MDL.Dkt.6444 at 10, but that is patently wrong. "The law of the case doctrine cannot be applied across distinct actions in [a] multidistrict

proceeding." *Home Depot USA, Inc. v. Lafarge N. Am., Inc.*, 59 F.4th 55, 61 (3d Cir. 2023).[34]

Issue preclusion likewise does not fit here. First, the "issue" is not the same—the district court held that specific, named general causation experts did not survive the application of *Daubert*. It never considered whether *other* experts could do so. This may well be the nub of the district court's error, since it repeatedly characterized the issue resolved by its order as "the theoretical potential of ranitidine to cause cancer," even though it was only supposed to be the resolution of a motion *in limine* to exclude particular evidence. MDL.Dkt.6622 at 5.

Second, plaintiffs who had not yet filed cases plainly fail the mutuality requirement, and the Supreme Court has rejected virtual representation or other end-runs around that longstanding element of issue preclusion. *See Taylor v. Sturgell*, 553 U.S. 880 (2008).[35] A "person who was not a party to a suit"—as later-filing plaintiffs undisputedly were not—"generally has not had a 'full and fair opportunity to litigate' the claims and issues settled in that suit." *Id.* at 892 (quoting *Montana v. United States*, 440 U.S. 147, 153-54 (1979)). The general fact that Plaintiffs'

[34] The district court's actions give strong support to the argument that it merged the cases, which destroyed diversity and the court's jurisdiction.

[35] Issue preclusion also cannot apply because there was no final judgment at the time the district court barred new plaintiffs from disclosing new experts. All the judgments were entered at the same time, and so preclusion from one of them could not affect any other.

Leadership litigated general causation makes no difference—the Supreme Court rejected issue preclusion in *Taylor* even though the second party had the same attorneys. *Id.* at 897.

Last, there is no free-floating MDL exception that supports the district court's decision. Section 1407 is a procedural provision allowing for "coordinated or consolidated pretrial proceedings" in a single venue, 28 U.S.C. §1407(a), but "[t]he MDL process 'does not merge the suits into a single cause, or change the rights of the parties, or make those who are parties in one suit parties in another.'" *Home Depot*, 59 F.4th at 62 (quoting *In re TMI Litig.*, 193 F.3d 613, 724 (3d Cir. 1999)). After all, "an MDL court's determination of the parties' rights in an individual case must be based on the same legal rules that apply in other cases, as applied to the record in that case alone." *In re Nat'l Prescription Opiate Litig.*, 956 F.3d 838, 841 (6th Cir. 2020). An MDL court does "not have the authority to create special rules" to "bind plaintiffs by the finding of previous proceedings in which they were not parties." *Home Depot*, 59 F.4th at 64 (quoting *In re TMI*, 193 F.3d at 726).

Appellants' proposed rule is eminently workable. MDL judges usually *do* allow plaintiffs to choose whether to use leadership's experts or their own, even after ruling on *Daubert*. *E.g.*, *In re Acetaminophen-ASD-ADHD Prod. Liab. Litig.*, No. 22-MC-3043, ECF No. 1408 (S.D.N.Y. Feb. 16, 2024) (allowing a new expert after excluding all of leadership's general causation experts). There is no reason to

fear that thousands of plaintiffs will irrationally spend millions of dollars to retain thousands of experts to litigate general causation seriatim—there is no incentive to do so. On the other side of the ledger, allowing the district court to deprive parties of their right to litigate their case violates fundamental principles of justice. In "administering a[n] MDL proceeding, due process and fundamental fairness may not be sacrificed to provide assembly-line justice." *In re Phenylpropanolamine (PPA) Prods. Liab. Litig.*, 460 F.3d 1217, 1250 (9th Cir. 2006).

IV. The District Court Erred In Dismissing Negligent Misrepresentation Claims By Consumers Of Generic Ranitidine Against Brand Defendants.

The MPIC included negligent misrepresentation claims against the Brand Manufacturers that plaintiffs who consumed generic ranitidine brought. Defendants moved to dismiss those claims to the extent the plaintiffs were harmed by generic ranitidine (a category they dubbed "innovator liability" claims), on the grounds that they owed no duty of care. MDL.Dkt.1585; MDL.Dkt.1973. Rather than address the motion with respect to particular cases, the district court requested two pages of briefing for each relevant state's law, MDL.Dkt.2228 at 2, MDL.Dkt.2307, MDL.Dkt.2335, then ruled that *no* state out of thirty-five would allow the claims, dismissing them on the merits, MDL.Dkt.2516.

The district court adopted Defendants' framework wholesale, presuming no duty would apply unless Plaintiffs cited a squarely on-point state supreme court decision. *See* MDL.Dkt.2516 at 14. The court also ruled that the injury to generic

consumers from brand-name manufacturers' deficient warning label was not even foreseeable, repeating cookie-cutter reasoning for every state based on a law review article by Victor Schwartz, the general counsel of the American Tort Reform Association. *E.g.*, MDL.Dkt.2516 at 26, 34, 37, 42, 47, 48, 50, 55, 60, 67, 70, 72, 74, 77, 78 (citing Victor E. Schwartz, *Warning: Shifting Liability to Manufacturers of Brand-Name Medicines When the Harm Was Allegedly Caused by Generic Drugs Has Severe Side Effects*, 81 Fordham L. Rev. 1835, 1865, 1870-71 (2013)). These overarching reasons predominated over state-specific analysis.

The district court also held that it lacked jurisdiction over claims brought under the laws of Massachusetts and California but allowed repleading. After Plaintiffs amended, the district court held that essentially every court lacks personal jurisdiction over claims under Massachusetts and California law. MDL.Dkt.3719 at 35-36.

While this Court "could make an *Erie* guess ... the more prudent course of action is to submit the issue to" the state supreme courts. *Pogue v. Oglethorpe Power Corp.*, 82 F.3d 1012, 1017 (11th Cir. 1996). That is what Appellants request where certification is available. Where it is not, rather than brief the tort law of thirty-five jurisdictions, Appellants highlight a cross-cutting methodological error in the district court's *Erie* predictions that warrants vacatur of the order and remand for a proper analysis. Last, the Court should reverse the district court's unprecedented and

clearly erroneous holding that it lacked personal jurisdiction over claims under California law.

A. The Court Should Certify the Question to State Courts.

The negligent misrepresentation claims at issue here follow from two unique features of the regulatory scheme for generic drugs that are unlike products in other industries. First, federal law places the ability to change the warnings for generic drugs into the hands of *brand-name* manufacturers. Second, state law allows—encourages, even—doctors to rely on the warnings and other medical information for brand-name drugs to recommend and prescribe brand-name drugs that can then be filled by pharmacists with a *generic* version. Under ordinary negligence principles, these features make the brand-name manufacturer the least-cost avoider, and the entity most responsible for harm. Despite that logic, a wall of federal precedent has rejected claims by generic consumers, largely because a leading case from the 1990s erred by denying the first feature. The result is an unjustified disparity between federal and state court that should be rectified.

1. Selling pharmaceuticals is only lawful with FDA approval.

The Federal Food, Drug, and Cosmetic Act 21 U.S.C. §301 *et seq.* (FDCA) sets the federal framework for pharmaceuticals. Selling even a perfectly safe and effective new drug without FDA pre-approval violates federal law. 21 U.S.C. §355(a). The manufacturer who develops a new drug—referred to as the brand-

name drug—must submit a New Drug Application (NDA) to the FDA. The FDA only approves a drug once it determines based on scientific evidence and data submitted by the NDA applicant that it is safe and effective. *Id.* §355(d); *see also Mut. Pharm. Co. v. Bartlett*, 570 U.S. 472, 476 (2013) ("for the FDA to consider a drug safe, the drug's 'probable therapeutic benefits must outweigh its risk of harm'" (quoting *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 140 (2000)). Once an NDA is approved, it comes with ongoing duties to send new and emerging scientific information about the risks of the approved drug to the FDA and to unilaterally update the drug's label when the evidence warrants a different warning. *See* 21 C.F.R. §314.70. These ongoing updates are a key pillar of drug safety. "[I]t has remained a central premise of federal drug regulation that the manufacturer," not the FDA, "bears responsibility for the content of its label at all times" and "is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market." *Wyeth v. Levine*, 555 U.S. 555, 570-71 (2009).

2. Brand-name manufacturers determine the content of generic drug label warnings.

After the brand-name manufacturer enjoys a period of highly profitable exclusivity, other drug manufacturers can file Abbreviated New Drug Applications (ANDAs) to sell a virtually identical drug called a generic. *See* 21 U.S.C. §355(j). Generic drugs may differ in certain respects from the branded drug (for example, the

expiration date), but the warnings and precautions, active ingredient, and dosage must be the same. *Id.* That means ANDA holders—the manufacturers of generic drugs—can only change their generic drug's warning label *after* a brand-name manufacturer does so. Any difference in labeling would not only violate federal law, it would also falsely imply a difference in risk, which would undermine the American system of using generic drugs as perfect substitutes for brand-name drugs.

The full implications of this regulatory regime were made clear when the Supreme Court held that—with respect to a drug that is legal to sell under federal law—certain failure-to-warn claims premised on the state-law duty to change a generic drug's warning label were *preempted*. *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 624 (2011). A generic drug company simply could not comply with such a state-law duty, since any change would make its generic drug warnings *different from* the brand-name drug it should match. The Supreme Court noted that to a consumer, the differing preemption result "makes little sense" since if a consumer took "the brand-name drug prescribed by their doctors" they could recover, but "because pharmacists, acting in full accord with state law, substituted [a] generic [drug] instead, federal law pre-empts these lawsuits." *Id.* at 625. Nonetheless, that is the law, which the Supreme Court reaffirmed in a follow-on case. *See Bartlett*, 570 U.S. at 493 (noting the difference in treatment was "tragic and evokes deep sympathy" but applying preemption).

3. State supreme courts recognize a duty on brand-name manufacturers for generic drug warnings.

Long before *Mensing*, some cases addressed whether brand-name manufacturers could be liable for injuries caused by generic drugs. The leading case was *Foster v. American Home Products Corp.*, 29 F.3d 165 (4th Cir. 1994), which predicted Maryland would answer "no." The Fourth Circuit, relying on the FDA's position at the time, held that *generic* manufacturers, not *brand-name* manufacturers, should be liable, because they *could* modify the warnings on their products. *Id.* at 170. A deluge of federal precedent followed *Foster*. But the premise was wrong: as *Mensing* made clear, generic manufacturers *cannot* control or change drug warnings.

After *Mensing* and *Bartlett*, the undermined cases remained in the Federal Reporter, and courts have been loath to change without new guidance. When this Court addressed the question of whether Florida would recognize a duty, it had an easy task: "[e]very court in Florida to consider the question" had rejected such a duty, which matched the federal cases. *Guarino v. Wyeth, LLC*, 719 F.3d 1245, 1251 (11th Cir. 2013). The only state *supreme* court to address the issue had found a duty, but had just granted rehearing, vacating the decision. *Id.* at 1253 (citing *Wyeth, Inc. v. Weeks*, No. 1101397, 2013 WL 135753 (Ala. Jan. 11, 2013), *opinion withdrawn and superseded*, 159 So. 3d 649 (Ala. 2014), *superseded by statute* Ala. Code §6-5-530(a)). A decade after *Guarino*, the landscape is quite different.

On rehearing, the Alabama Supreme Court resoundingly recognized a duty under traditional state common law applied to "a product that, unlike any other product on the market, has unprecedented federal regulation." *Wyeth, Inc. v. Weeks*, 159 So. 3d 649, 677 (Ala. 2014), *superseded by statute*, Ala. Code § 6-5-530(a) ("nor are we creating a now tort of 'innovator liability' as has been suggested"). The Alabama state legislature later statutorily abrogated Alabama's common law, granting special immunity to brand-name manufacturers. *See* Ala. Code §6-5-530(a).

The next state supreme court to address the issue was Iowa's. It ruled against recognizing a duty, but by a 3-1-3 vote in which the controlling concurrence "agree[d] with much of the dissent on the claims against the brand defendant, but decline[d] at this time to conclude the public policy considerations that ultimately drive the decision in this case, on balance, support the imposition of a duty of care." *Huck v. Wyeth, Inc.*, 850 N.W.2d 353, 381 (Iowa 2014) (Cady, C.J. concurring). Iowa's law, then, is that no duty exists "at this time," as of 2014.

In light of *Mensing* and *Weeks*, the Fourth Circuit was no longer confident in its leading *Foster* precedent, because "it is no longer the case that generic manufacturers can alter FDA-approved labels." *McNair v. Johnson & Johnson*, 694 F. App'x 115, 120 (4th Cir. 2017). It therefore certified the question of duty to the

West Virginia Supreme Court. That court declined to recognize a duty in a 3-2 decision the next year. *Id.*, 818 S.E.2d 852 (W. Va. 2018).

California came next. It held unanimously that brand-name manufacturers *do* have a duty to consumers of generic drugs for a number of reasons, chiefly foreseeability and the fact that "[t]he brand-name drug manufacturer is the only entity with the unilateral ability to strengthen the warning label" and so should have a duty "to prevent a known or reasonably knowable harm" only it can prevent. *T.H. v. Novartis Pharms. Corp.*,407 P.3d 18, 32 (Cal. 2017).

The most recent decision came from Massachusetts. The Supreme Judicial Court *unanimously*—and contrary to the predictions of three federal courts—held that brand-name manufacturers had a duty to consumers of generic drugs. *Rafferty v. Merck & Co.*, 92 N.E.3d 1205 (Mass. 2018). The Massachusetts court did, however, require recklessness, rather than mere negligence. *Id.* at 1219.

4. This Court should certify the question.

This is exactly the situation for which certification is appropriate. Most federal cases have predicted state courts would not recognize the duty at issue here, though the vast majority of those cases came before 2017. Whether due to defendants' removal of cases or some other reason, most state court systems have never considered the question; in fact, of the five state supreme courts to address it, two—Alabama and West Virginia—were answering a question certified by a federal

court. That is backwards. *State* courts should determine *state* law. That is why this Court has never "hesitated to pull" the tool of certification "out of our toolbox," and has "employed the certification procedure more than any other circuit," with "no apologies for having done so." *Pittman v. Cole*, 267 F.3d 1269, 1290 (11th Cir. 2001).

"Where there is *any doubt* as to the application of state law, a federal court *should* certify the question to the state supreme court to avoid making unnecessary *Erie* 'guesses' and to offer the state court the opportunity to interpret or change existing law." *CSX Transp., Inc. v. City of Garden City*, 325 F.3d 1236, 1239-40 (11th Cir. 2003) (quoting *Mosher v. Speedstar Div. of AMCA Int'l, Inc.*, 52 F.3d 913, 916-17 (11th Cir. 1995)) (emphasis added). This Court teaches that the "'most important' factors in deciding to certify are 'the closeness of the question and the existence of sufficient sources of state law ... to allow a principled rather than conjectural conclusion.'" *Blackburn v. Shire US Inc.*, 18 F.4th 1310, 1322 (11th Cir. 2021) (quoting *Florida ex rel. Shevin v. Exxon Corp.*, 526 F.2d 266, 274-75 (5th Cir. 1976)).

Here, state courts have not had the "opportunity" to develop their law, and that paucity leaves this Court with great difficulty in divining any "principled" way to distinguish among the states. Most of the states at issue have no cases whatsoever—even at the trial level—on the question of whether brand-name

manufacturers owe a duty of care to generic consumers.[36] The only certainty here is that not all states would reject the theory: when state supreme court justices *have* ruled, comfortably more than a filibuster-proof majority—25 out of 34—have recognized a duty.[37] The cases ruling against a duty have been on the slimmest of margins and have recognized that the question is close.

Alabama, Massachusetts, West Virginia, and Iowa lacked appellate case law on the issue before their supreme courts took up the question for the first time. Three federal courts predicted Massachusetts would not recognize the theory; one even declined to certify the question, believing it could make an "informed and intelligent prediction" due to the supposedly "overwhelming and well-reasoned majority view, which has been set out in multiple opinions by a variety of federal and state courts." *In re Zofran (Ondansetron) Prods. Liab. Litig.*, 261 F. Supp. 3d 62, 82 (D. Mass. 2017). Federal courts were right to think the issue was not close, but 180 degrees wrong about the direction—the Massachusetts Supreme Judicial Court ruled

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[36] Defendants' briefing appeared to count just 4 states in which any state-court case had considered and rejected these claims—13 states have neither state nor federal case law, and the other 18 have only federal cases or case law that *favors* a duty. *See* MDL.Dkt.2335 at 2; *see also* MDL.Dkt.2307 (Plaintiffs' briefing).

[37] *See McNair*, 818 S.E.2d at 867 (**2-3** against a duty); *Rafferty*, 92 N.E.3d 1205 (**7-0** in favor of a duty); *T.H.*, 407 P.3d 18 (**7-0** in favor of a duty); *Huck*, 850 N.W.2d at 356 (**3** in favor, **3** against, **1** "concur[ring] in the result only," opposing a duty "at this time"); *Weeks*, 159 So. 3d 649 (**6** in favor, **2** against, **1** (not counted) dissenting on the non-merits ground that fact-specific issues warranted dismissing the certified question).

unanimously to allow the claim. That stunning mis-prediction should awaken the federal courts from their dogmatic slumber.

It is time, at long last, for this question of state common law to be resolved at the proper level in our cooperative federalist system: the state supreme courts. Only certification can avoid the embarrassment of blanket, implausible predictions like the order below. Plaintiffs request certification of the following question:

> Under [state] law, does a brand-name drug manufacturer owe a duty of care under negligence principles to a consumer of a generic version of the drug based on the inadequate warnings crafted by the brand-name manufacturer, and copied onto the generic label?

The following states permit certification of questions from this Court:

Alaska: Alaska R. App. P. 407.

Arizona: Ariz. Rev. Stat. §12-1861.

Arkansas: Arkansas Sup. Ct. R. 6-8.

Colorado: Colo. App. R. 21.1.

Connecticut: Conn. Gen. Stat. §51-199b.

Delaware: Del. Const. art. 4, §11 and Del. S. Ct. R. 41.

District of Columbia: D.C. Code §11-723.

Hawaii: Haw. Rev. Stat. §602-5 and Haw. R. App. P. 13.

Maine: Me. Rev. Stat. tit. 4, §57.

Maryland: Md. Code, Cts. & Jud. Proc. §12-603.

Michigan: Mich. Ct. R. 7.308.

Minnesota: Minn. Stat. §480.065, subd. 3.

Mississippi: Miss. R. App. P. 20.

Montana: Mont. R. App. P. 15.

Nebraska: Neb. Rev. Stat. §24-219.

Nevada: Nev. R. App. P. 5.

New Hampshire: N.H. Sup. Ct. R. 34.

New Mexico: N.M. Stat. §39-7-4 and N.M. R. App. P. 12-607.

New York: N.Y.C.P.L.R. §500.27.

North Dakota: N.D. R. App. P. 47.

Oklahoma: 20 Okla. Stat. tit. 20, §1602.

Oregon: Or. Rev. Stat. §28.200.

Pennsylvania: 210 Pa. Stat. and Consol. Stat. §3341.

Puerto Rico: P.R. Laws tit. 4, §24s.

Rhode Island: R.I. Super. Ct. R., art. 1, Rule 6.

South Carolina: S.C. App. Ct. R. 244.

South Dakota: S.D. Codified Laws §15-24A-1.

Utah: Utah Code §78A-3-102 and Utah R. App. P. 41.

Vermont: Vt. R. App. P. 14.

Virginia: Va. Const. art. 6, §1 and Va. Sup. Ct. R. 5:40.

Wisconsin: Wis. Stat. §821.01.

Wyoming: Wyo. R. App. P. 11.01.

B. The District Court Erred in Applying a Federal Common Law Presumption.

Illinois, Missouri, and North Carolina do not appear to allow certification from this Court. For these states, this Court should clarify the legal standard for *Erie* predictions. Defendants argued, and the lower court accepted, that in performing an *Erie* guess, "federal courts sitting in diversity should not expand the scope of tort liability without a clear signal from the state courts." MDL.Dkt.1585 at 12. Again, Defendants argued below: "Plaintiffs have the burden to identify an authoritative case in each state that ***directly*** recognizes a claim by generic product consumers against the Brand-Name Manufacturer Defendants." MDL.Dkt.2335 at 16. This argument is commonly called "*Erie* conservatism" by the defense bar.[38] This error infected enough federal cases that the California Supreme Court lamented that "federal decisions" in this area are "of little use in discharging our task" because they have "operat[ed] under a presumption against expanding liability." *T.H.*, 407 P.3d at 38. To state the obvious, no similar presumption applies in state court, and

[38] *See*, *e.g.*, James M. Beck, *Federal Courts Should Remember Federalism*, Drug & Device Law (Nov. 28, 2006), https://www.druganddevicelawblog.com/2006/11/federal-courts-should-remember.html ("When a state-law action proceeds in federal court, the jurisprudential thumb is planted firmly on the scale to weigh against novel expansions of state law.").

such a presumption does not even purport to come from state law. Instead, it can only be a federal common law rule of decision. Applying this presumption would plainly produce forum shopping. Though cloaked in the false garb of federalism and judicial modesty, Defendants' true principle is a barefaced rejection of *Erie*. It cannot stand.

1. Federal Courts Must Employ an Evenhanded *Erie* Guess.

When sitting in diversity, federal courts apply state substantive law. *Erie R.R. Co. v. Tompkins*, 304 U.S. 64, 78 (1938). On questions of state law, this Court is bound by the rulings of state supreme courts. Where a state's highest court has not addressed a question, "federal courts are bound by decisions of a state's intermediate appellate courts unless there is persuasive evidence that the highest state court would rule otherwise." *Bravo v. United States*, 577 F.3d 1324, 1325 (11th Cir. 2009) (quoting *King v. Order of United Com. Travelers of Am.*, 333 U.S. 153, 158 (1948)). When there is no state decision on point, a federal court must act as a state court would, predicting as best it can how the state's highest court would rule. *Id.* at 1325-26 (noting "it is the duty" of the court, which is "forced" to "ascertain" what state law is based on "all available data" (quoting *West v. Am. Tel. & Tel. Co.*, 311 U.S. 223, 237 (1940), and *Putman v. Erie City Mfg. Co.*, 338 F.2d 911, 917 (5th Cir. 1964))); *see Turner v. Wells*, 879 F.3d 1254, 1262 (11th Cir. 2018) (same). Even with no guidance from a state's highest court, federal judges need not sink their

heads in the sand, presuming that an absence of applicable precedent is evidence the state court would reject a position; after all, "[f]ederal courts, when sitting in diversity, are no ostriches." *Lupu v. Loan City, LLC*, 903 F.3d 382, 395 (3d Cir. 2018). Like all good forecasters, a federal court must act under uncertainty rather than abdicating whenever the answer is unclear.

A proper prediction of state law must be guided by the foundational principles *Erie* laid down. Prior to *Erie*, federal courts discerned general law by their own lights, in the process creating yawning gaps between the results in federal court and those in state court. The regime of *Swift v. Tyson*, 41 U.S. 1 (1842), "made rights enjoyed under the unwritten 'general law' vary according to whether enforcement was sought in the state or in the federal court; and the privilege of selecting the court in which the right should be determined was conferred upon the noncitizen." *Erie*, 304 U.S. at 74-75. *Erie* ended that paradigm definitively:

> Except in matters governed by the Federal Constitution or by acts of Congress, the law to be applied in any case is the law of the state. And whether the law of the state shall be declared by its Legislature in a statute or by its highest court in a decision is not a matter of federal concern. **There is no federal general common law**.

Id. at 78 (emphasis added).

Because there is no federal general common law, no federal rules of decision exist that could decide a diversity case differently from how it would be decided in state court. The absence of any federal rules of decision plays an important practical

role in preventing any difference in result between federal and state court deriving from substantive law. Indeed, the very "nub of the policy that underlies [*Erie*] is that for the same transaction the accident of a suit by a non-resident litigant in a federal court instead of in a state court a block away, should not lead to a substantially different result." *Van Dusen v. Barrack*, 376 U.S. 612, 638 (1964) (quoting *Guar. Trust Co. of N.Y. v. York*, 326 U.S. 99, 109 (1945)). Ensuring that any difference in results in federal and state court do not derive from the substantive law applied in the forum fulfills "the twin aims of the *Erie* rule: discouragement of forum-shopping and avoidance of inequitable administration of the laws." *Hanna v. Plumer*, 380 U.S. 460, 468 (1965). Any principle purporting to guide an *Erie* prediction that promotes forum shopping or derives from federal common law not only lacks a basis in *Erie* or federalism, but actively undermines both.

2. The district court applied a federal presumption against liability that finds no support in state law.

The district court relied heavily on a presumption that a state court would not expand liability. It received only two pages of briefing on each state's law, but ruled that *no undecided state* would recognize a duty, and emphasized that "[t]his prediction comports with the principles of comity and federalism," by which it meant *refusing to expand liability* comports with comity and federalism. MDL.Dkt.2516 at 14-15. Defendants' briefing asked the court to do just this, claiming that "Plaintiffs have the burden to identify an authoritative case in each state that ***directly***

recognizes a claim by generic product consumers against the Brand-Name Manufacturer Defendants." MDL.Dkt.2335 at 16 (emphasis added).

The principle the district court applied is *Erie* conservatism—that is, the notion that federal courts should predict a state supreme court would *reject* liability whenever no clear precedent affirmatively supports liability. *Erie* conservatism is an illicit federal common law rule of decision. Like any substantive legal presumption,[39] such a principle must be grounded in a source of law. Any *state*-law presumption would apply only to *Erie* predictions concerning that state, and would derive not from federalism or judicial restraint, but simply the law of that state. A state-law presumption could be proper, but few (if any) states endorse such a principle. Neither Appellees nor the district court provided any state-law authority for such a presumption, and many states, such as Illinois, emphatically reject it.[40]

Necessarily, because it purportedly applies to *all Erie* predictions in federal court, *Erie* conservatism must derive from *federal* law rather than state law. Yet that

[39] The presumption cannot be procedural, since it relates wholly to the law to be applied in the case, not the rules of the forum, and it governs primary conduct rather than the litigation itself.

[40] Even in rejecting market-share liability, the court defended its progressive bona fides: "We have not in the past been hesitant to develop new tort concepts[.]" *Smith v. Eli Lilly & Co.*, 560 N.E.2d 324, 344-45 (Ill.1990). Its public policy recognizes "the fundamental premise of tort law—that of just compensation for any loss or injury proximately caused by the tortfeasor." *Clark v. Children's Mem'l Hosp.*, 955 N.E.2d 1065, 1073 (Ill. 2011).

cannot be. No statute or constitutional provision requires it. And *Erie* itself makes crystal clear that *there is no general federal common law*, with no special exception for anti-liability presumptions. When courts apply *Erie* conservatism, they are, whatever their protests, drawing on the law of the brooding omnipresence above each federal courthouse—the law of nowhere. *Cf. S. Pac. Co. v. Jensen*, 244 U.S. 205, 222 (1917) (Holmes, J., dissenting) ("The common law is not a brooding omnipresence in the sky, but the articulate voice of some sovereign or quasi sovereign that can be identified[.]"). The Supreme Court has made clear that federal courts may not refrain from deciding state law questions "merely because the answers to the questions of state law are difficult or uncertain or have not yet been given by the highest court of the state." *Meredith v. City of Winter Haven*, 320 U.S. 228, 234-35 (1943). This principle applies equally to the practice of using a presumption to resolve cases.

Worse still, *Erie* conservatism inevitably induces forum shopping. That is so because it artificially pushes any prediction errors in one direction: in favor of the defendant. A state court may be equally likely to rule for the plaintiff or defendant on an unsettled question—or, in some states such as Illinois, may be much more likely to resolve uncertainties in the plaintiff's favor—but a federal court would always resolve uncertainty in the defendant's favor. Defendants are no less able to discern advantages in federal court now than they were in the era of *Swift v. Tyson*.

Employing presumptions that skew results defies *Erie* rather than implementing it. *See* Abbe R. Gluck, *Intersystemic Statutory Interpretation: Methodology as "Law" and the Erie Doctrine*, 120 Yale L.J. 1898, 1937-40 (2011) (criticizing *Erie* conservatism because "it explicitly encourages forum shopping").

Beyond applying a federal rule of decision and promoting forum shopping, employing a presumption against liability badly impairs the accuracy of federal court guesses. No betting man would employ the strategy of favoring one result whenever the outcome is uncertain. Consider someone trying to forecast the results of an election. Polls would be the best evidence of what would happen, much like lower court cases are the best evidence of how a state's supreme court would rule. But some elections have no polls. *Erie* conservatism is much like a forecaster who, whenever no polls exist for a race, ignores demographic information and correlations with *other* state's polling, in favor of mechanically guessing that the incumbent candidate will win. Such a guess will be right *sometimes*, but will predictably misfire in a number of contests. Employing no presumption at all, and instead simply looking at all available evidence is a superior strategy both in predicting elections and state supreme court rulings.

The district court's analysis clearly misfired. Consider Illinois. The two Illinois courts to consider the question—both in Zantac cases—have held that the Illinois Supreme Court would recognize a duty. *See Bayer v. Boehringer Ingelheim*

Pharm. Inc., No. 2021-L-915 (Madison Cnty. Cir. Ct. March 24, 2022); *Banna v. Walgreen Co.*, No. 2020-L-004916 (Cook Cnty. Cir. Ct. Aug. 25, 2023) (consolidated proceeding with *all* Illinois Zantac cases). All *federal* courts in Illinois have agreed with the Illinois state courts. *See Garner v. Johnson & Johnson*, No. 1:16-cv-01494, 2017 WL 6945335, at *7 (C.D. Ill. Sept. 6, 2017) (Darrow, J.); *Dolin v. GlaxoSmithKline LLC*, 269 F. Supp. 3d 851, 864 (N.D. Ill. 2017) (Hart, J.) (adhering to Judge Zagel's ruling); *Dolin v. SmithKline Beecham Corp.*, 62 F. Supp. 3d 705, 713 (N.D. Ill. 2014) (Zagel, J.), *rev'd on other grounds sub nom. Dolin v. GlaxoSmithKline LLC*, 901 F.3d 803 (7th Cir. 2018); *see also In re Fluoroquinolone Prods. Liab. Litig.*, No. 0:15-MD-02642, 2021 WL 396819, at *9 (D. Minn. Feb. 4, 2021) (adopting *Dolin* and rejecting the opinion below). Only the opinion below and the Sixth Circuit have disagreed. *See In re Darvocet, Darvon, and Propoxyphene Prods. Liab. Litig.*, 756 F.3d 917, 944 (6th Cir. 2014).

The district court rested its contrary prediction on a supposed product identification requirement and on the facially bizarre argument that injury to consumers of generic ranitidine is not foreseeable (an argument for which the district court cited a tort reform advocate). *See* MDL.Dkt.2516 at 37 (citing Schwartz). The *Dolin* case explains the flaw in the product identification argument. *See* 62 F. Supp. 3d at 713. Though the Illinois legislature passed a tort reform bill in 1995 that codified product liability law in a way that would have subsumed claims like these,

the Illinois Supreme Court struck it down as unconstitutional (discussed below). *Id.* Negligent misrepresentation claims have their own elements and need not satisfy the requirements of product liability law (such as product identification).

As for Mr. Schwartz' foreseeability argument, whatever his persuasiveness in other contexts, his record in predicting or stating *Illinois* law on torts is abysmal. He wrote an article on why the Illinois General Assembly's 1995 tort reform should be—and would be—upheld by the Illinois Supreme Court against legal challenge. *See* Victor E. Schwartz, *Illinois Tort Law: A Rich History of Cooperation and Respect Between the Courts and the Legislature*, 28 Loy. U. Chi. L. J. 745 (1997). "Clearly," he wrote, "the Act reflects sound public policy and is consistent with Illinois legal history." *Id.* at 760. The Illinois Supreme Court cited and refuted his article, holding that the "statutory cap on compensatory damages for noneconomic losses"—the very same cap he suggested is "clearly ... sound public policy"—was "arbitrary" and therefore unconstitutional (together with the *entire* tort reform law). *Best v. Taylor Mach. Works*, 689 N.E.2d 1057, 1077 (Ill. 1997). Victor Schwartz—who the district court repeatedly relied upon[41]—said this foundational opinion

[41] MDL.Dkt.2516 at 26, 34, 37, 42, 47, 48, 50, 55, 60, 67, 70, 72, 74, 77, 78 (all citing Schwartz).

"overreach[ed]" and "ignored the fundamental separation of powers principle upon which our entire system of government is based."[42]

The Illinois Supreme Court struck down a *second* tort reform law twenty years later. It held that "reducing the systemic costs of tort liability was [in]sufficient ... [because] the entire burden of any cost savings would impermissibly rest on one class of injured plaintiffs." *Lebron v. Gottlieb Mem'l Hosp.*, 930 N.E.2d 895, 905 (Ill. 2010). To this day, the American Tort Reform Association—whose general counsel is one Victor Schwartz—deems Illinois a "judicial hellhole," and claims it is "a preferred jurisdiction for plaintiffs' lawyers thanks to no-injury lawsuits, plaintiff-friendly rulings in asbestos litigation, and the promise of a liability-expanding legislative agenda each and every year."[43] Relying on an anti-liability presumption and scholarship by an avowed critic of the Illinois tort system resulted in an erroneous prediction.

Brand-name pharmaceutical manufacturers told federal courts for years that no state supreme court would impose a duty. Scores of federal courts agreed, predicting time after time that no state would allow these claims. At least three

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[42] Victor E. Schwartz, et al., *Fostering Mutual Respect and Cooperation between State Courts and State Legislatures*, 103 W. Va. L. Rev. 1, 9-10 (2000).

[43] American Tort Reform Foundation, *Judicial Hellholes 2020/2021* (Dec. 2020) https://www.judicialhellholes.org/wp-content/uploads/2020/12/ATRA_JH20_layout_09d-1.pdf.

federal courts ruled that Massachusetts would reject the theory. *E.g.*, *In re Darvocet, Darvon & Propoxyphene Prod. Liab. Litig.*, No. 2:11-MD-2226, 2012 WL 3610237, at *2-3 (E.D. Ky. Aug. 21, 2012), *aff'd* 756 F.3d 917 (6th Cir. 2014); *Patterson v. Novartis Pharm. Corp.*, 451 F. App'x 495, 497 (6th Cir. 2011); *In re Zofran (Ondansetron) Prod. Liab. Litig.*, 261 F. Supp. 3d at 78. This was a bad guess—the Supreme Judicial Court of Massachusetts *unanimously recognized* a duty on brand-name manufacturers. *Rafferty*, 92 N.E.3d at 1219. Plaintiffs from Massachusetts were injured by drug company misrepresentations, then lost their case merely because they were forced into a hostile federal forum that misstated Massachusetts law. The same thing is happening here.

3. Federal courts cannot bootstrap themselves into a consensus.

This district court was clearly impressed by the volume of federal precedents, but the apparent majority position is built on sand. Nearly all cases decided the issue before federal courts realized that generic manufacturers could not change drug warnings, a rule that was cemented within a day of *Guarino* with the Supreme Court's ruling in *Bartlett*, 570 U.S. 472. Even in 2017, the Fourth Circuit—home of the once-leading case rejecting a duty on brand-name manufacturers that had been contradicted by *Mensing*—deemed the question uncertain enough to be certified to the Supreme Court of West Virginia. *McNair*, 694 F. App'x at 119-20.

Since that time, Iowa, West Virginia, California, and Massachusetts each reached the question, and the results were nothing like the consensus in federal court: they split 50/50. In terms of state jurists, the pro-liability side won 25 to 9. Lord John Maynard Keynes is quoted as saying "When the facts change, I change my mind. What do you do, sir?"[44] Federal courts should give their best prediction of how the state supreme courts would rule, with no thumb on the scale. A bad guess is a bad guess, and earns no extra points for being "conservative."

* * *

No evenhanded application of *Erie* could result in a prediction that all 35 jurisdictions at issue would reject Appellants' claims. That kind of patently erroneous prediction is only possible by applying the presumption that Defendants argued strongly for in their briefing: an anti-liability presumption in the absence of clear state law. This Court should set forth the proper standard for an *Erie* guess—namely, an evenhanded *prediction* based on all available evidence—vacate, and remand.

C. The District Court Erred in Holding That it Lacked Personal Jurisdiction over Claims under California and Massachusetts Law.

In a break from every court that has ever considered the question, the district court held that no court even has specific personal jurisdiction to adjudicate claims

[44] Jason Zweig, *Keynes: He Didn't Say Half of What He Said. Or Did He?*, Wall St. Journal (Feb. 11, 2019) https://www.wsj.com/articles/BL-MB-32547.

under California and Massachusetts law. MDL.Dkt.3719 at 35-36. This holding amounts to a *per se* rule that states cannot allow generic consumers to sue brand-name manufacturers for their negligence unless the defendant is headquartered in the state. It smacks of the long-discredited era in which courts routinely struck down laws that abridged judicial notions of substantive due process. Fortunately, the Supreme Court has rejected that view of personal jurisdiction. The district court's holding is irreconcilable with *Ford Motor Co. v. Montana Eighth Judicial District Court*, 592 U.S. 351 (2021), and should be reversed.

Personal jurisdiction requires two prongs. First, the defendant must have taken "some act by which [it] purposefully avails itself of the privilege of conducting activities within the forum State." *Id.* at 352. Second, "[t]he plaintiff 's claims ... 'must arise out of or relate to the defendant's contacts' with the forum." *Id.* at 359 (citation omitted). There need not be any "causal relationship between the defendant's in-state activity and the litigation." *Id.* at 362; *see also id.* at 361 (holding that the "causation-only approach" "finds no support in [the] Court's" cases). Even if "the plaintiff's claims 'would be precisely the same if [the defendant] had never done anything in [the forum]," that is still not enough to defeat personal jurisdiction. *Id.* at 366. Both prongs are met here.

1. The AMPIC alleges purposeful availment.

There is no dispute "that Defendants purposefully availed themselves 'of the privilege of conducting activities' within California and Massachusetts"—indeed, their activities were "pervasive in the forum states." MDL.Dkt.3719 at 26-27 (citation omitted). The district court even agreed that "litigation" in the forum was "reasonably foreseeable." *Id.* at 28 (quoting *Oldfield v. Pueblo de Bahia Lora, S.A.*, 558 F.3d 1210, 1221, 1223 (11th Cir. 2009)). The district court accepted the AMPIC's allegations:

> Plaintiffs allege that Defendants "targeted the California and Massachusetts markets" by: (i) employing large forces of salespersons to educate physicians about the Zantac label and to promote prescriptions of the drug; (ii) conducting research and studying market share and consumer purchasing of brand-name and generic ranitidine products; (iii) contracting with social media outreach firms to increase targeted advertising and marketing efforts; (iv) conducting medical studies and scientific seminars and/or attempting to influence the medical profession; (v) advertising via television, radio, and newspaper to promote the sale of Zantac; and (vi) contracting with retailers and wholesalers to expand their Zantac business. [AMPIC] ¶232(a)-(f). For each of these general activities, Plaintiffs provide examples of how and when one or more of Defendants undertook such activities.

Id. at 10-11.

2. Brand-Name Manufacturers' contacts are related to the claims.

The district court summarized the AMPIC allegations detailing why the contacts were related to the claims:

> Plaintiffs allege that Defendants negligently and recklessly misrepresented the safety and efficacy of ranitidine products "to Plaintiffs via the media, advertising, website, social media, packaging, and promotions" and intended for Plaintiffs and/or their physicians to rely upon those misrepresentations. [AMPIC] ¶¶2684-88, 2709, 2718. Plaintiffs allege that but for those misrepresentations, Plaintiffs would not have been prescribed, purchased, or consumed generic ranitidine products and would not have been injured. *Id.* ¶¶2690-91

Id. at 12; *see also id.* at 26. That is more than enough for personal jurisdiction under *Ford*.

Brand Defendants—not generics—advertised; their representations—not generics'—were in the widely used Physician's Desk Reference (PDR); they—not generics—crafted the warning label. MDL.Dkt.2759 ¶¶2676-78. Any of the Brand Manufacturers could have cured the misrepresentations about Zantac's safety, but never did. The generic manufacturers were required to and did copy the misrepresentations the Brand Manufacturers repeatedly made. *Id.* ¶2678. Customers and doctors relied on the Brand Manufacturers' safety information, advertising, and reference materials—for example, under California law, a doctor deciding whether to prescribe ranitidine would have information from GSK (*e.g.*, in the Physician's Desk Reference), would write a prescription for "Zantac," but it would be "the pharmacist who actually decides whether the patient receives the brand-name drug

or its generic bioequivalent"—whose label the prescribing doctor may never have read. *T.H.*, 407 P.3d at 30 (citing Cal. Bus. & Prof. Code §4073).

Based on the facts, the relation is obvious. Brand Defendants marketed, sold, and vouched for the label for branded Zantac in California; they knew full well that they were similarly vouching for the label for generic ranitidine sold in California. 21 C.F.R. §314.94(a) (generic label's warnings must exactly match the brand-name label). When they failed to mention cancer risk in their label, they ensured that generic consumers in California would similarly be deprived of this crucial information—and "[b]ut for the Brand-Name Manufacturer Defendants failure to tell Plaintiffs the truth about the safety and composition of ranitidine-containing products, Plaintiffs would not have consumed or purchased them." MDL.Dkt.2759 ¶2690.

The district court ignored this clear relation by shrinking down the contacts to those with a but-for causal relationship with the cause of action in the abstract. On its reasoning, the "only conduct that gives rise to Plaintiffs' claims is Defendants' alleged failure to update the warning label," and so "other activities do not relate to the claim." MDL.Dkt.3719 at 29-30. After limiting its consideration to "the one forum-based contact that *does* clearly relate to an innovator-liability claim—labeling decisions" it held that jurisdiction was lacking because "Defendants' labeling

decisions regarding brand-name ranitidine products [did not] occur[] in California or Massachusetts." *Id.* at 31.

This holding falls apart even on its own terms. To start, *T.H. v. Novartis* would come out the other way, since Novartis is a Swiss company, and plainly does not make its "labeling decisions" in California. Worse, the rationale would seem to limit jurisdiction for *every* negligent misrepresentation claim to the place where the "misrepresentation decisions" were made, rather than where plaintiffs *read* the misrepresentation and *were harmed* by it. In fact, it is difficult to see why ordinary failure-to-warn claims would escape—surely GSK makes its "warning decisions" at its headquarters, and sells drugs only indirectly, through distributors and retailers. True, GSK advertises and develops the California market, but those efforts are irrelevant to the claim on the district court's test because the exact same failure-to-warn claim would exist *without* any advertising.

California courts have had no trouble seeing this holding for what it is: the "jurisdictional challenge is, in actuality, a challenge 'aimed at California's warning label liability law.'" *Rosewolf v. Merck & Co.*, 635 F. Supp. 3d 830, 838 (N.D. Cal. 2022) (quoting *Whaley v. Merck & Co.*, No. 3:21-cv-1985, 2022 WL 1153151, at *8 (S.D. Cal. Apr. 12, 2022)). And they have had no trouble expressly rejecting the flaw in the district court's argument: "*Zantac* in effect improperly applied the strict

causation test that *Ford* rejected." *Haddad v. Merck & Co.*, No. 22-cv-151, 2022 WL 17357779, at *6 (C.D. Cal. Aug. 11, 2022).

This Court has rejected the district court's approach: "In performing the minimum contacts analysis, we identify *all contacts* between the nonresident defendant and the forum state and ask whether, individually or collectively, those contacts satisfy the relevant criteria. As noted earlier, the nonresident's contact with the forum *need not give rise to the plaintiff's claim*." *Del Valle v. Trivago GmbH*, 56 F.4th 1265, 1276 (11th Cir. 2022) (emphasis added) (citations omitted). The district court did exactly the opposite: it first isolated the "only conduct that *gives rise to Plaintiffs' claims*"—namely, the "failure to update the warning label,"—then concluded that "other activities do not relate to the claim." MDL.Dkt.3719 at 29-30 (emphasis added).

This Court's rule follows from *Ford*. There, the Court explained: "so what if (as *Walden* held) the place of a plaintiff's injury and residence cannot create a defendant's contact with the forum State? Those places still may be relevant in assessing the link between the defendant's forum contacts and the plaintiff 's suit—including its assertions of who was injured where." 592 U.S. at 371. Just so here. So what if the Plaintiffs' residence and injury *in California* cannot create the Brand Defendants' contact—they are still relevant in linking the many contacts they did have to the claim. This Court also highlighted that "Ford's attempt to serve the

Montana market by aggressively advertising there constituted an 'activity or an occurrence' in Montana," even though the plaintiffs in *Ford* bought the vehicle in a different state, meaning the advertisements did not directly relate to the suit (and obviously were not required to state a claim under Montana law). *Herederos de Roberto Gomez Cabrera, LLC v. Teck Res. Ltd.*, 43 F.4th 1303, 1311 n.3 (11th Cir. 2022).

The district court essentially held that California and Massachusetts tort law is unconstitutional. This Court should vacate that erroneous ruling.

3. If the court indeed lacked personal jurisdiction, its merits rulings must be vacated.

Other than a few brand-loyal consumers or those who stopped taking ranitidine before 1995, essentially every plaintiff at some point consumed generic ranitidine, and many took generic ranitidine exclusively. If the district court is correct that it lacked personal jurisdiction for claims based on generic ranitidine, then those claims can be filed in a venue that would have jurisdiction (for example, Delaware or Pennsylvania[45]).

a. Claims under California or Massachusetts law can be refiled.

Appellants anticipate that Appellees may argue that the Court should not reach the question of whether the district court had personal jurisdiction, because it can

[45] Brand-Name Defendants have consented to suit in Pennsylvania. *See Mallory v. Norfolk S. Ry. Co.*, 600 U.S. 122 (2023).

uphold summary judgment based on *Daubert*. That is not correct. A without-prejudice dismissal under Rule 12(b)(2) is far different from a preclusive merits ruling under Rule 56. A court without personal jurisdiction cannot enter judgments on the merits—if that is what the court did, this Court should vacate. *Courboin v. Scott*, 596 F. App'x 729, 735 (11th Cir. 2014) ("we affirm ... lack of personal jurisdiction ... and we vacate the part of the district court's order" addressing the merits); *Marsalis v. STM Reader, LLC*, 806 F. App'x 748, 752-53 (11th Cir. 2020) (vacating merits ruling because "reach[ing] the merits ... was error" without "personal jurisdiction"); *Cosmichrome, Inc. v. Spectra Chrome, LLC*, 504 F. App'x 468, 471-72 (6th Cir. 2012) (same); *One Techs., LLC v. Amazon.com, Inc.*, 860 F. App'x 785, 788 (2d Cir. 2021) (same). This makes a practical difference for Appellants—if this Court affirms the district court's personal jurisdiction ruling, Appellants can refile their claims based on generic ranitidine in a forum with personal jurisdiction.

b. Claims under the other 35 jurisdictions' laws were on the merits, but, alternatively, should be vacated if there was no personal jurisdiction.

Appellees may also ask that the Court sidestep the merits rulings on the generic consumers' negligent misrepresentation claims by saying the district court was without personal jurisdiction. The Court should likewise reject this argument. It is beyond question that a court without jurisdiction cannot rule on the merits.

Sinochem Int'l Co. v. Malaysia Int'l Shipping Corp., 549 U.S. 422, 430-31 (2007). Brand Defendants knew that when they asked the district court to rule for them on the merits for 35 jurisdictions, and on personal jurisdiction in 2. No defendant can "simultaneously seek affirmative relief from a court," such as dismissal on the *merits*, "and object to that court's exercise of jurisdiction." *S.E.C. v. Ross*, 504 F.3d 1130, 1148 (9th Cir. 2007). Defendants asked for, and received, a merits ruling, and therefore consented to the district court's jurisdiction.

If the Court disagrees, it must vacate the district court's extensive 35-jurisdiction merits ruling *and* its *Daubert* ruling for these claims. Any merits ruling was *ultra vires* if the court lacked jurisdiction. The Court should then direct a dismissal without prejudice, leaving Appellants free to refile these claims in a proper court.

CONCLUSION

The district court apparently decided it was done with this litigation, crafting a *Daubert* order of prodigious length, stuffing it with alternative holdings, and granting summary judgment in every case (in addition to any other bases for dismissal). That is not the proper judicial role under *Daubert*. And it is not the proper role of an MDL judge, who has a duty to give each litigant his own day in court. This Court should either vacate for lack of jurisdiction, or (if the Court reaches the merits), reverse and remand for further proceedings.

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Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limitation allowed by this Court's Order, Dkt.137-1 at 3, because it contains 27,970 words, excluding the parts exempted by Fed. R. App. P. 32(f).

This brief complies with the typeface requirements of Fed. R. App. P. 32(a) because it has been prepared in a proportionately spaced typeface using Microsoft Word Times New Roman 14-point font.

Dated: April 10, 2024

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CERTIFICATE OF SERVICE

On April 10, 2024, I electronically filed the foregoing with the Clerk of the Court for the United States Court of Appeals for the Eleventh Circuit by using the CM/ECF system. All participants in this case are registered CM/ECF users, and service will be accomplished by the CM/ECF system.

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